# SERUM TITANIUM ESTIMATION IN POSTOPERATIVE INDIVIDUALS WITH TITANIUM IMPLANT USING INDUCTIVELY COUPLED PLASMA MASS SPECTROMETRY AND ITS CLINICAL CORRELATION

*Dissertation submitted in*
*Partial fulfillment of the regulations required for the award of*

**M.S. DEGREE in**
**ORTHOPAEDIC SURGERY**

**THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY**

**COIMBATORE-TAMILNADU**

**APRIL 2019**

# Coimbatore Medical College

**COIMBATORE, TAMILNADU, INDIA - 641 014**

(Affiliated to The Tamilnadu Dr. MGR Medical University, Chennai)

## ETHICS COMMITTEE

## CERTIFICATE

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| **Period of Study** | : | **1 year** |
| **College** | : | **Coimbatore Medical College & Hospital.** |
| **Dissertation Topic** | : | **Serum Titanium estimation in post operative individuals with titanium implant using inductively coupled plasma mass spectrometry and its clinical correlation.** |

**The Ethics Committee, Coimbatore Medical College has decided to inform that your Dissertation Proposal is accepted and you are permitted to proceed with the above Study.**

24.12.16

*Member Secretary*
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# CERTIFICATE

This is to certify that this dissertation titled **"Serum titanium estimation in postoperative individuals with titanium implant using inductively coupled plasma mass spectrometry and its clinical correlation"** is a bonafide record of work done by **Dr.Shreyas Doddihithlu,** during the period of his post graduate study from May 2016 to September 2018 under guidance and supervision in the INSTITUTE OF ORTHOPAEDICS AND TRAUMATOLOGY, Coimbatore Medical College and Hospital, Coimbtore-641018, in partial fulfilment of the requirement for **M.S.ORTHOPAEDIC SURGERY** degree examination of The Tamilnadu Dr. M.G.R. Medical University to be held in April 2019.

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# DECLARATION

I declare that the dissertation entitled **"SERUM TITANIUM ESTIMATION IN POSTOPERATIVE INDIVIDUALS WITH TITANIUM IMPLANT USING INDUCTIVELY COUPLED PLASMA MASS SPECTROMETRY AND ITS CLINICAL CORRELATION"** submitted by me for the degree of M.S, ORTHOPAEDIC SURGERY is the record work carried out by me during the period of **May 2016 to September 2018** under the guidance of **Prof.Dr.S.Vetrivel Chezian, M.S.Ortho.,D.Ortho., FRCS, PhD,** Head of the Departmetnt, Institute of Orthopaedics and Traumatology, Coimbatore Medical College & Hospital, Coimbatore. This dissertation is submitted to the Tamilnadu Dr.M.G.R. Medical University, Coimbatore, in partial fulfillment of the University regulations for the award of degree of M.S.ORTHOPAEDICS examination to be held in April 2019.

Place: Coimbatore
Date:

**Signature of the Candidate**

**(Dr.Shreyas Doddihithlu)**

Signature of the Guide
**Prof.Dr.S.Vetrivel Chezian, M.S.Ortho.,D.Ortho., FRCS, PhD,**
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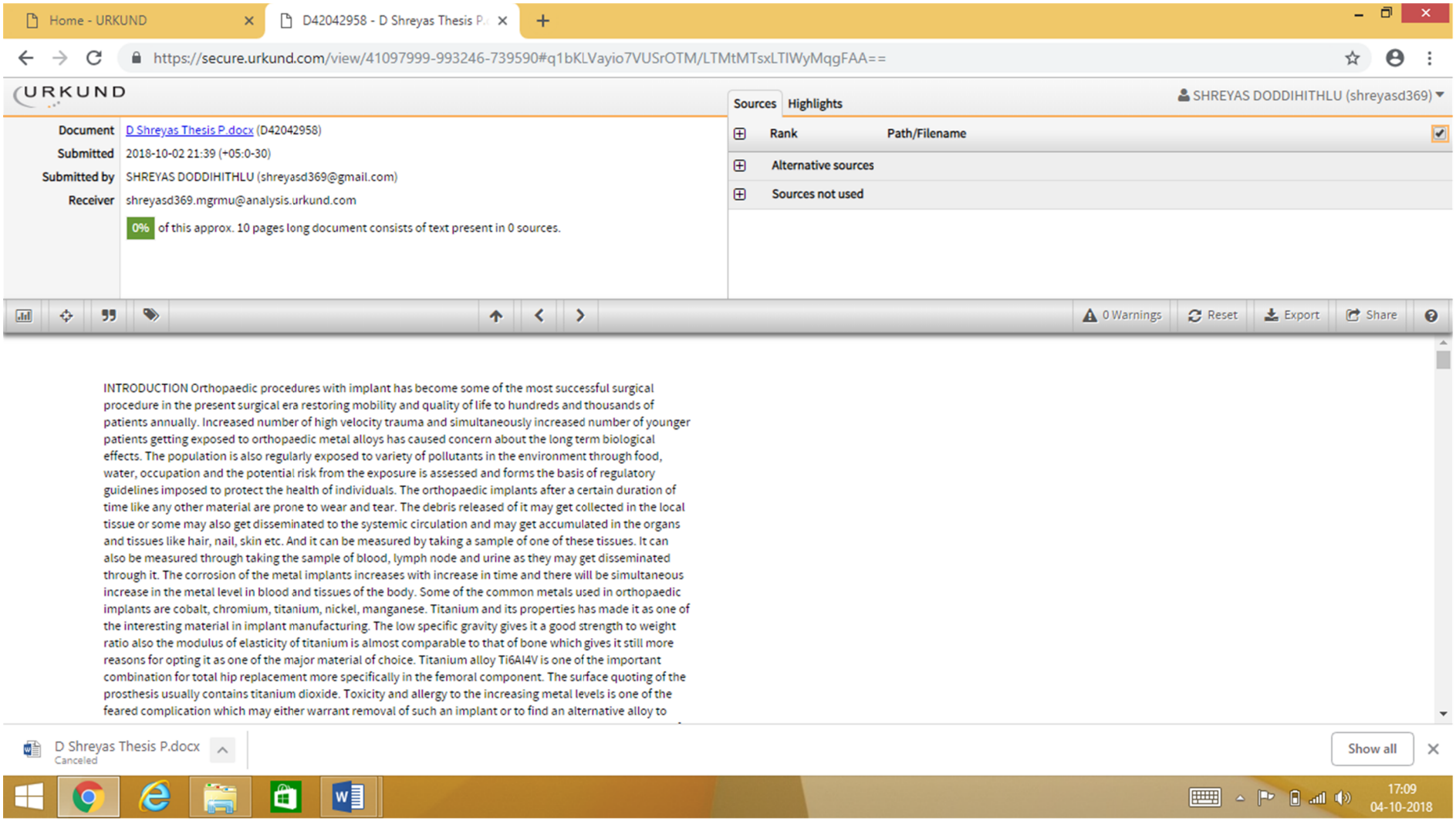
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INTRODUCTION Orthopaedic procedures with implant has become some of the most successful surgical procedure in the present surgical era restoring mobility and quality of life to hundreds and thousands of patients annually. Increased number of high velocity trauma and simultaneously increased number of younger patients getting exposed to orthopaedic metal alloys has caused concern about the long term biological effects. The population is also regularly exposed to variety of pollutants in the environment through food, water, occupation and the potential risk from the exposure is assessed and forms the basis of regulatory guidelines imposed to protect the health of individuals. The orthopaedic implants after a certain duration of time like any other material are prone to wear and tear. The debris released of it may get collected in the local tissue or some may also get disseminated to the systemic circulation and may get accumulated in the organs and tissues like hair, nail, skin etc. And it can be measured by taking a sample of one of these tissues. It can also be measured through taking the sample of blood, lymph node and urine as they may get disseminated through it. The corrosion of the metal implants increases with increase in time and there will be simultaneous increase in the metal level in blood and tissues of the body. Some of the common metals used in orthopaedic implants are cobalt, chromium, titanium, nickel, manganese. Titanium and its properties has made it as one of the interesting material in implant manufacturing. The low specific gravity gives it a good strength to weight ratio also the modulus of elasticity of titanium is almost comparable to that of bone which gives it still more reasons for opting it as one of the major material of choice. Titanium alloy Ti6Al4V is one of the important combination for total hip replacement more specifically in the femoral component. The surface quoting of the prosthesis usually contains titanium dioxide. Toxicity and allergy to the increasing metal levels is one of the feared complication which may either warrant removal of such an implant or to find an alternative alloy to
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**(Dr.Shreyas Doddihithlu)**

# CONTENTS

# INTRODUCTION

Orthopaedic procedures with implant has become some of the most successful surgical procedure in the present surgical era restoring mobility and quality of life to hundreds and thousands of patients annually. Increased number of high velocity trauma and simultaneously increased number of younger patients getting exposed to orthopaedic metal alloys has caused concern about the long term biological effects. The population is also regularly exposed to variety of pollutants in the environment through food, water, occupation and the potential risk from the exposure is assessed and forms the basis of regulatory guidelines imposed to protect the health of individuals.

The orthopaedic implants after a certain duration of time like any other material are prone to wear and tear. The debris released from it may get collected in the local tissue or some may also get disseminated to the systemic circulation and may get accumulated in the organs and tissues like hair, nail, skin etc. And it can be measured by taking a sample of one of these tissues. It can also be measured through taking the sample of blood, lymph node and urine as they may get disseminated through it. The corrosion of the metal implants increases with increase in time and

there will be simultaneous increase in the metal level in blood and tissues of the body.

Some of the common metals used in orthopaedic implants are cobalt, chromium, titanium, nickel, manganese. Titanium and its properties has made it as one of the interesting material in implant manufacturing. The low specific gravity gives it a good strength to weight ratio also the modulus of elasticity of titanium is almost comparable to that of bone which gives it still more reasons for opting it as one of the major material of choice[1]. Titanium alloy **Ti6Al4V** is one of the important combination for total hip replacement more specifically in the femoral component. The surface quoting of the prosthesis usually contains titanium dioxide.

Toxicity and allergy to the increasing metal levels is one of the feared complication which may either warrant removal of such an implant or to find an alternative alloy to serve the same purpose. Toxic levels are usually predetermined and periodic supervision over the increase of the levels may help to know not only about the toxic alert but also as an indirect sign for the loosening of or excessive wear out of the implant. Some surgeons consider it as one of the hints along with radiological and clinical signs for planning a revision surgery.

The degradation products of the implants used in orthopaedic implants basically exist in two forms: soluble also called as ionic and particle debris. The soluble type which is called as the ionic form is found to be attached to the serum protein specifically or nonspecifically. The local response to the implant is one of the major type which is initiated by the activation of macrophages. Systemic reaction is also seen in some patients.

The concern about the release of soluble metal ions like Titanium(Ti), chromium(Cr), cobalt(Co), vanadium(V) are always to be kept in mind. Maximum amount of these metal ions are found in the pseudocapsules surrounding the implant. Cobalt, chromium, vanadium are some among the trace metals which are important for normal homeostasis.

# AIMS AND OBJECTIVES

## AIM

Serum titanium estimation in postoperative individuals with titanium implant using inductively coupled plasma mass spectrometry and its clinical correlation.

## OBJECTIVE

1. To look for increase in serum level of Titanium in individuals with titanium implants in relation to time.
2. To look for any toxicity signs and symptoms.

# REVIEW OF LITERATURE

The use of metals in the medicine have been made hundreds and thousands of years ago. Metallic silver was used by the Chaldeans was dated 4000BC.

For the purpose of reducing infections gold and copper were used as antimicrobials. To preserve water Greeks, Romans, Egyptians used silver. Silver nitrate was used to treat surgical wounds, skin ulcers and compound fractures [2].

Earliest use of metal as an implant was dated back to 2000 years ago where Romans, Chinese used gold in dentistry.

Europeans used iron for replacement of tooth around 200 AD [3]. Incas in the ancient times used silver and gold plates to repair cranial defects [4].

In 1886 metal plates were used for the first time in the internal fixation of fractures. But the problem of infection and corrosion was of greatest troubling issue.

Later in 1924 the discovery of stainless steel allowed the use of implant in the body without much problems and at a reasonable cost.

Introduction of cobalt in 1936 became one of the most popular metal implant in orthopaedic surgery [5].

In later part of that century the discovery of titanium, nickel, vanadium also revolutionised the orthopaedic implant armamentarium.

J. Jacobs et al[6] in the year 1990 stated that the increased serum titanium level in patients who had total hip replacement is suggestive of aseptic loosening. The patients who had well-functioning total hip replacement did not have any significant increase in titanium concentration. He also suggested that attempts to quantitate periarticular debris on the basis of either histological scales are of limited clinical value. So levels in serum and urine as well as in remote tissues may be of more biological importance.

Nadim J Hallab[7] in 2009 mentioned that it is unable to predict which patients will be prone and who are not for the implant debris induced inflammation. But some of the likely factors are:

- Greater number of particles are more proinflammatory
- Elongated particle fibres are generally more proinflammatory than the round particles.
- More chemically reactive particles are more proinflammatory than others.

# PATHOPHYSIOLOGY

Immunity

It is the ability of ones body to react and protect itself against foreign particles like bacteria, fungus, virus or any other toxic substances that enter the body and cause harmful effect [8].

Susceptibility is the term which is used if an individual is prone for a particular pathogen.

There are mainly two types of immunity :

1) Innate immunity

2) Acquired immunity

## INNATE IMMUNITY

I. Anatomical defence

II. Phagocytic defence

III. Blood protein defence

IV. Cytokines

Anatomical defence include the skin due to its acidic environment inhibits growth of microrganisms. Mucus membrane also acts as a anatomical barrier.

Phagocytic defence includes

i. Neutrophils
ii. Macrophages
iii. Natural killer cells

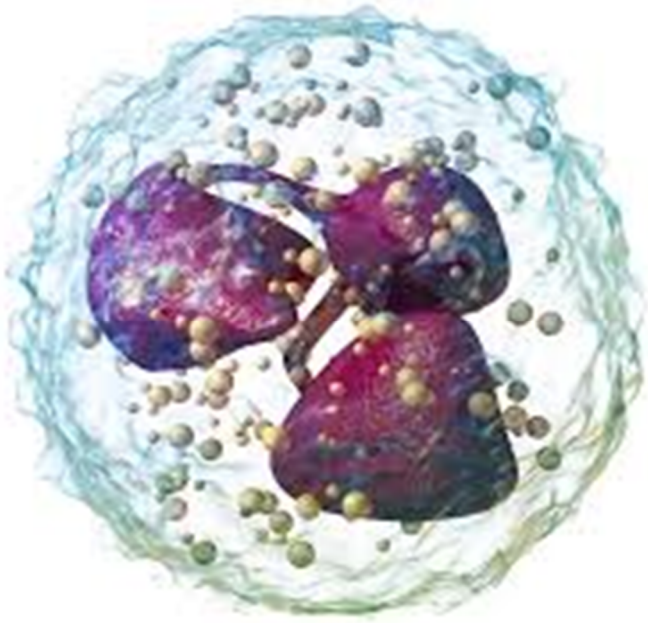
**NEUTROPHILS**

It constitutes of 60-70 % of circulating leucocytes in human body. Has got important role in inflammatory responses that are critical for host defense against infection. It acts by phagocytosis.

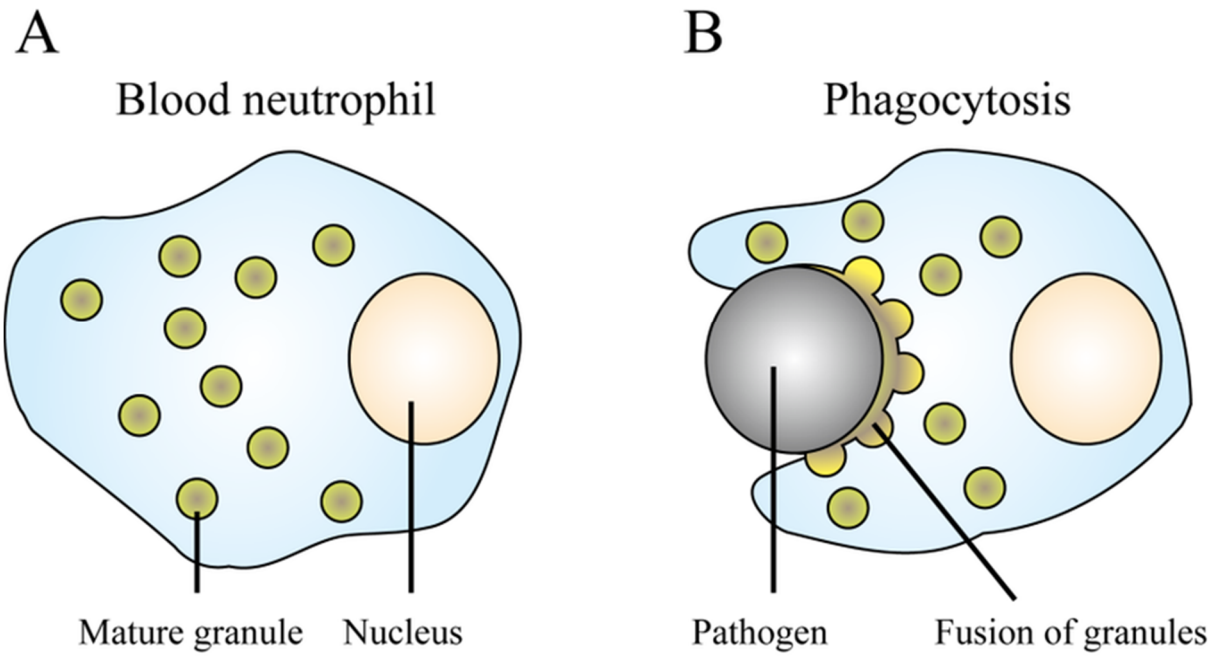
**MACROPHAGE**

These are the professional phagocytes and are the antigen presenting cells. They also have secretory function as one of the main function which will mediate the inflammatory process [9].

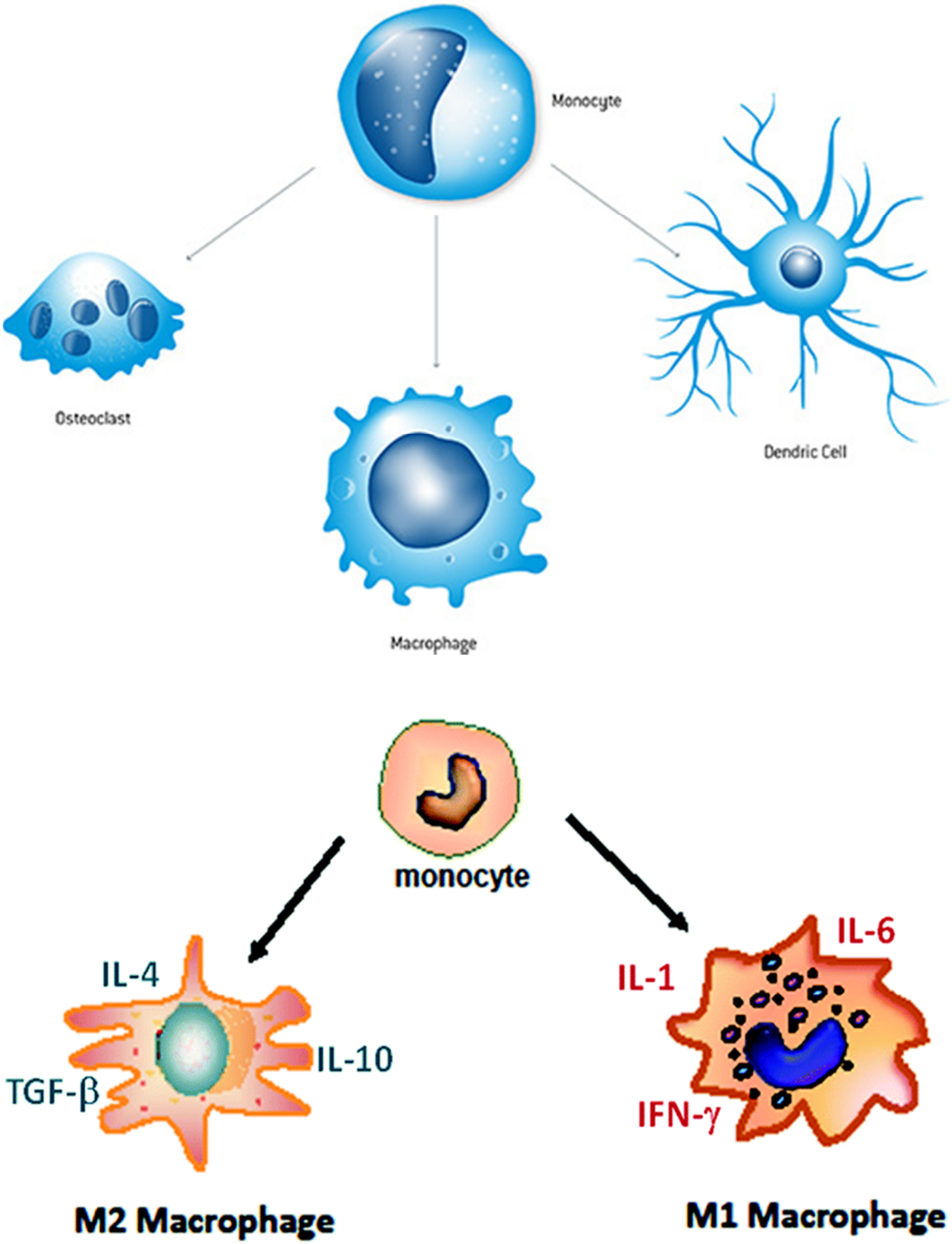
They also carry receptors for lymphokines that gives them the ability to get activated against tumour cells. They can get differentiated to other forms depending on the tissue where they are present and can be called by different names.



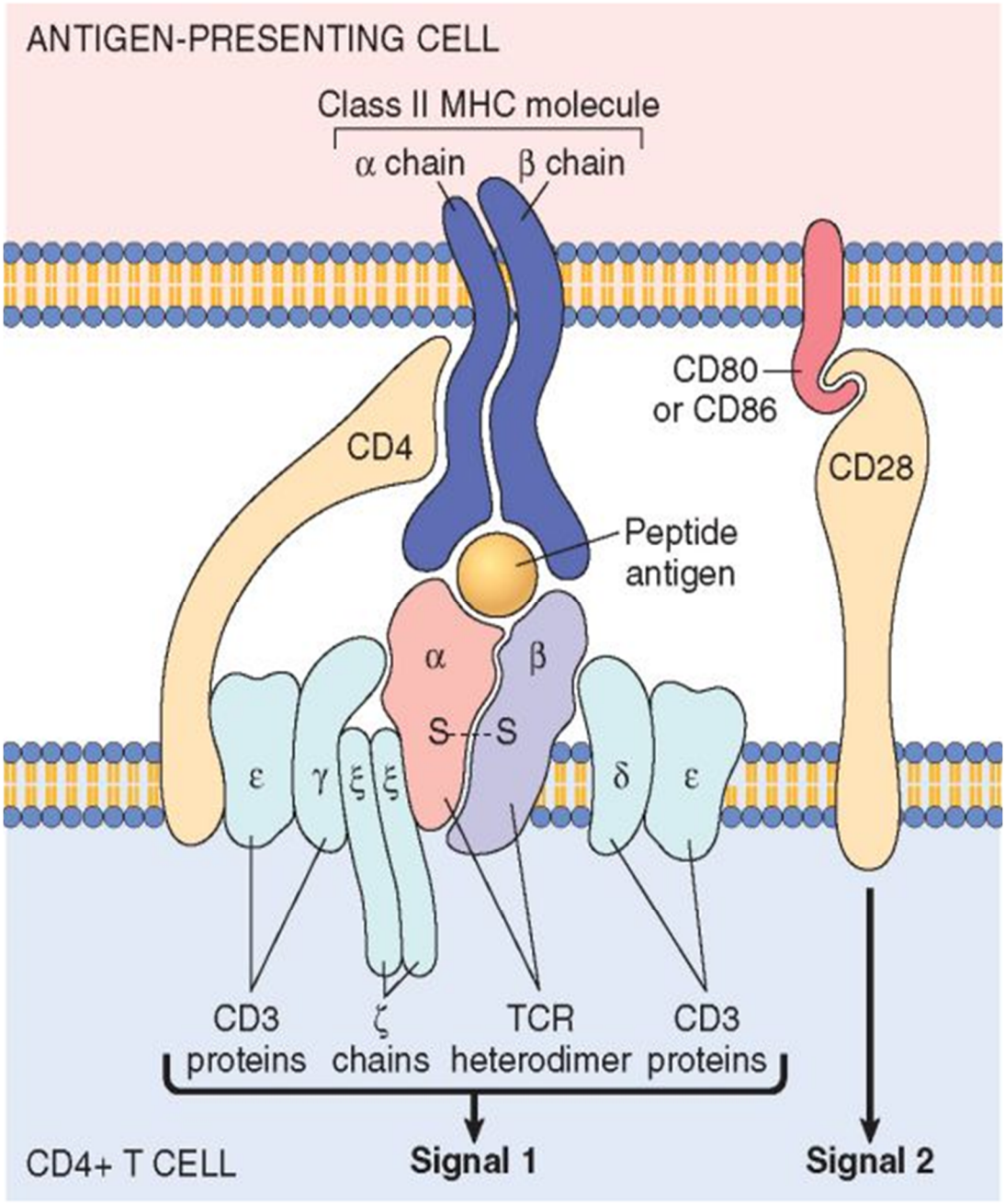
Neutrophil



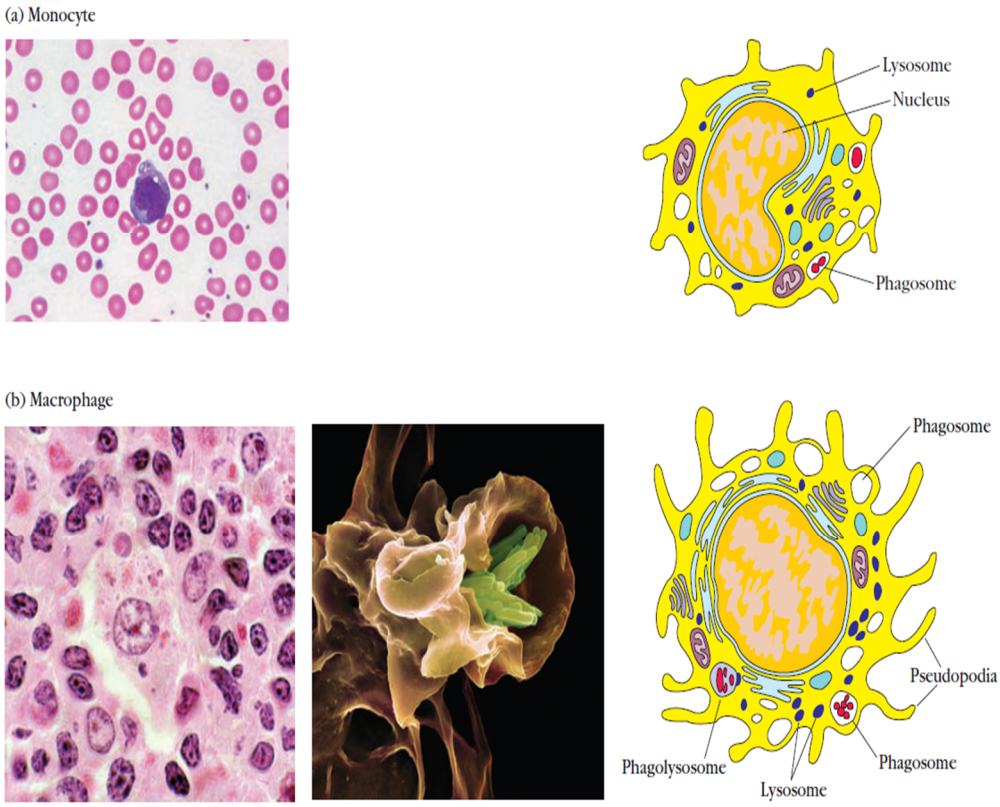

a. Neutrophil b. Phagocytosis




**IL – Interleukin, TGF – Transforming growth factor, IFN – Interferon, Macrophage and cytokine production**



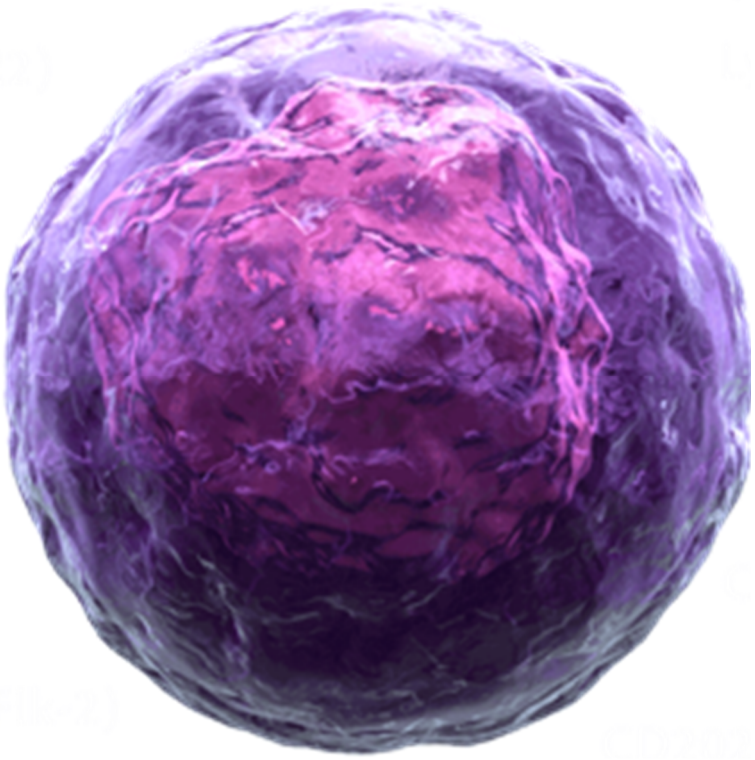

**Major Histocompatibility Complex signalling model**



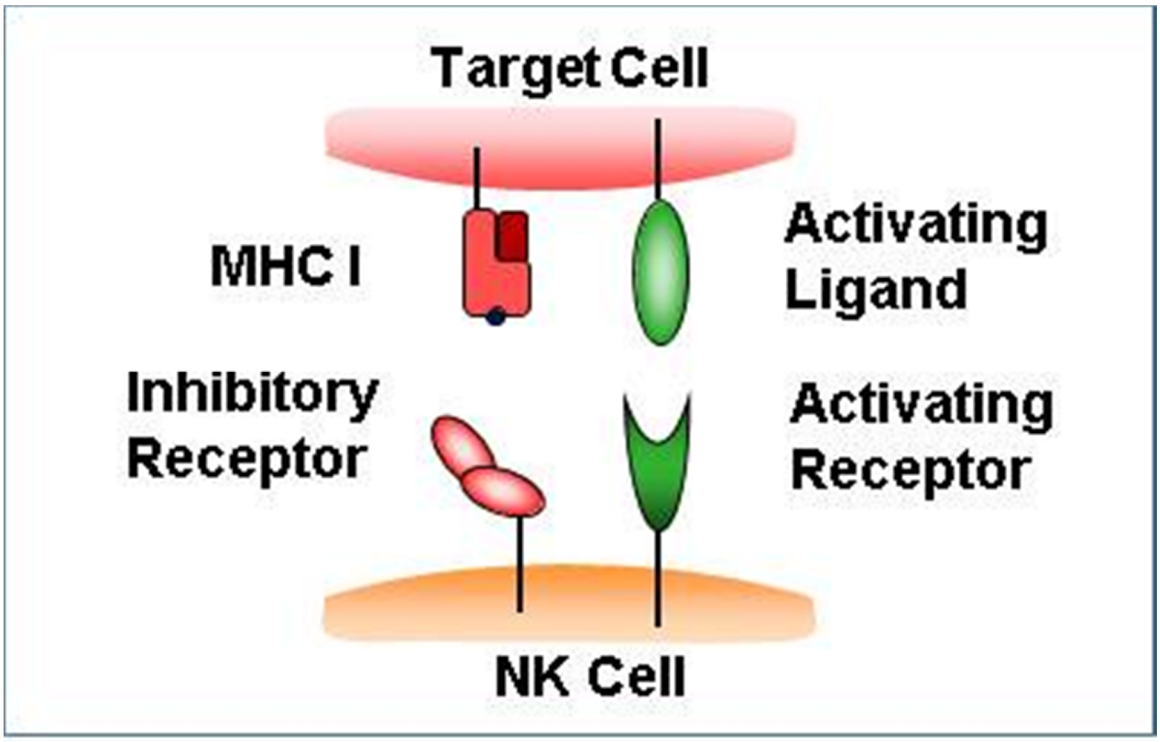

a. Monocyte b. Macrophage

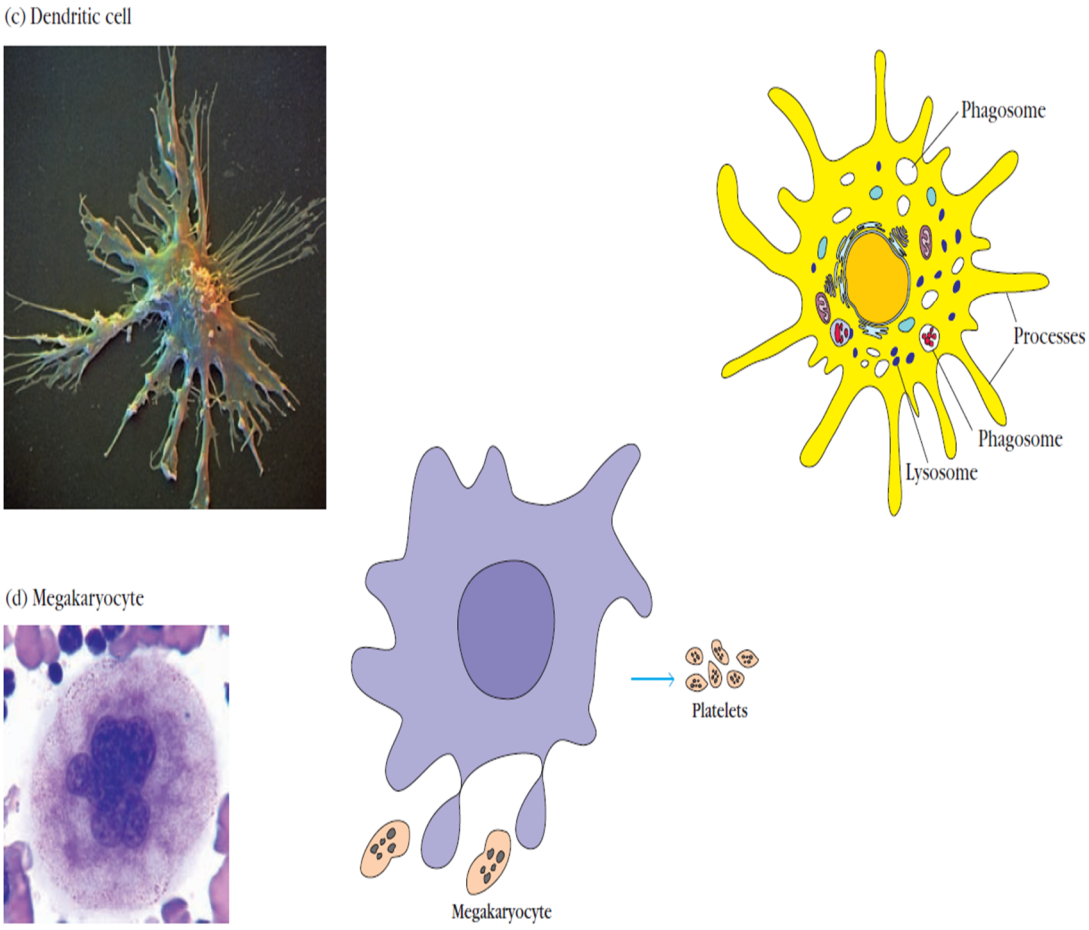
## NATURAL KILLER CELLS

These are the granular lymphocytes in which the granules are large and are derived from lymphoblasts. These cells are cytotoxic. The granules in these cells release perforins and proteases which are called as the granzymes which will cause apoptosis of the targeted cells.



**Natural killer cell**






c. Dendritic cell d. Megakaryocyte

## CYTOKINES

These are the molecules secreted by the cells of the immune system for communication of the signal. They are attached to the surface receptors of the cells/pathogens and help in the action of the immune system.

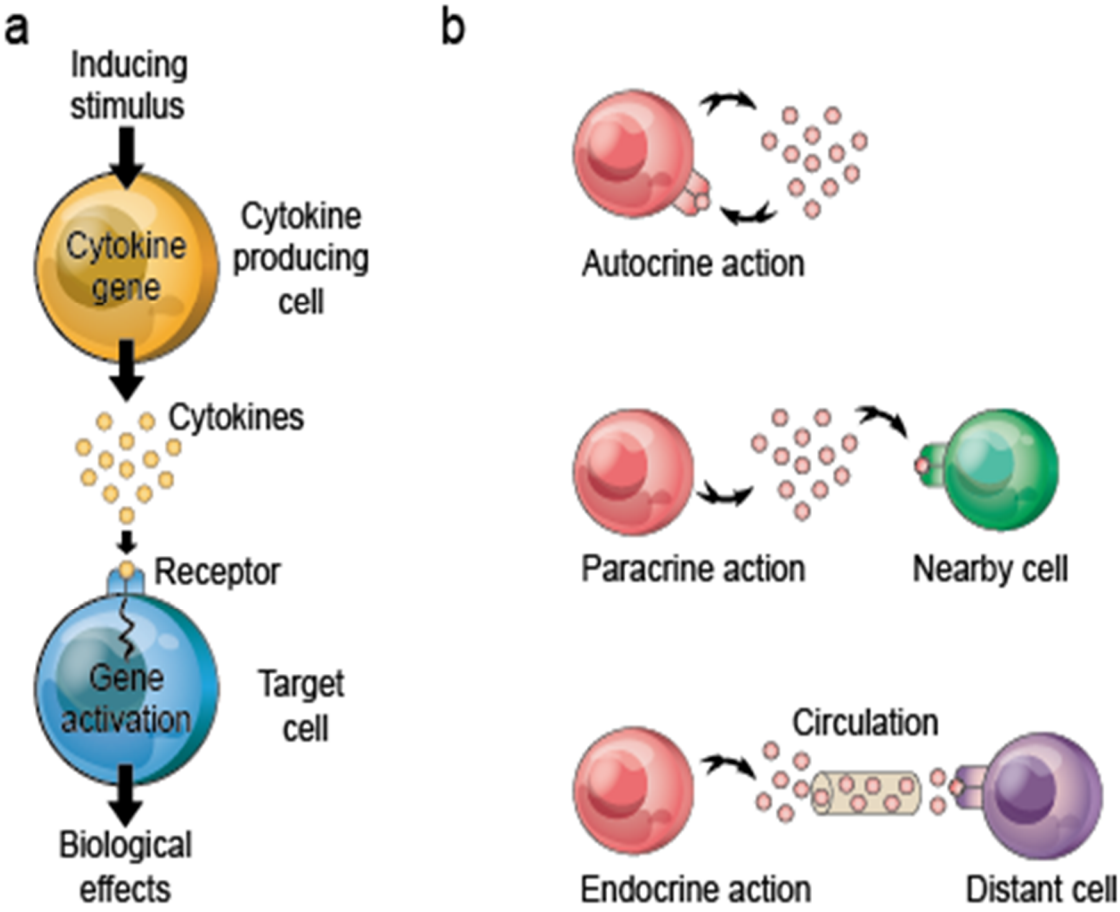
Cytokines are a group of protein molecules which are of low molecular weight also called as glycoprotein which are secreted in response to a particular type of stimuli [10].

Three types of action noted

i. Autocrine – Cytokine may bind to the surface of the same cell exerting its action

ii. Paracrine – Cytokine bind to the target cell which is nearby to the cell which has produced it thereby exerting its action

iii. Endocrine – It travels to bind to the target cell in the distant part of the body thereby exerting its action.

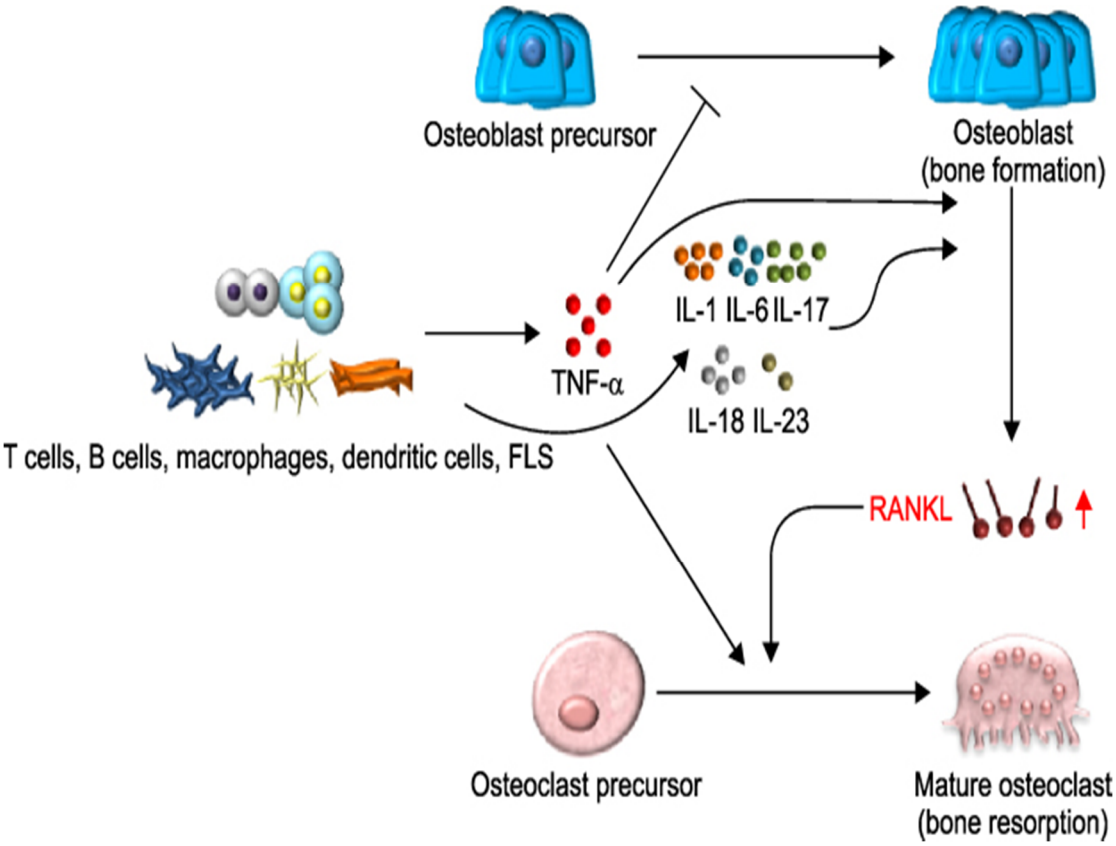


Macrophages, osteoblast and also fibroblasts that are exposed to the debris of the metal will stimulate the innate immunity against the metal particles. Some of the chemokines that are important in the aseptic loosening of the implant are interleukin 8, monocyte chemoattractant protein 1. Interleukin 8 is upregulated by monocyte and macrophages present around the implant site due to various metal particles like cobalt, chromium, titanium. Due to these cytokines macrophages and osteoclasts are attracted to the implant site and this will lead to osteolysis.. Increased production of monocyte chemoattractant protein 1 was also seen from the fibroblasts after they come in contact with titanium and polymethyl methacrylate (PMMA).

Osteoclasts also express tartarate resistant acid phosphatase(TRAP) and vitronectin receptor (VNR) this will be located on the bone soft tissue interface that is usually at the bone implant junction. There are also evidence invitro studies showing bone resorbing activities of the macrophages is reasonable showing ontogenic relationship with the osteoclasts. Osteoclasts have the capacity to phagocyte a variety of wear particles like ceramics, metallic or polymers. After the process of phagocytosis these cells remain as normal hormone sensitive and functional cells.

Osteoblasts are sensitised by the wear particles and they start producing the osteoclastogenesis factor such as the RANKL and chemokines like interleukin 6 & 8 . There will also be increased expression of vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMP 1).

Soft tissue cells like fibroblast will also secrete interleukin 1 beta ,interleukin 6 &8 , cyclooxygenase 1 &2 , transforming growth factor beta . Stimulated fibroblasts express RANKL and osteoprotegrin causing stimulation of the inflammatory cycle.

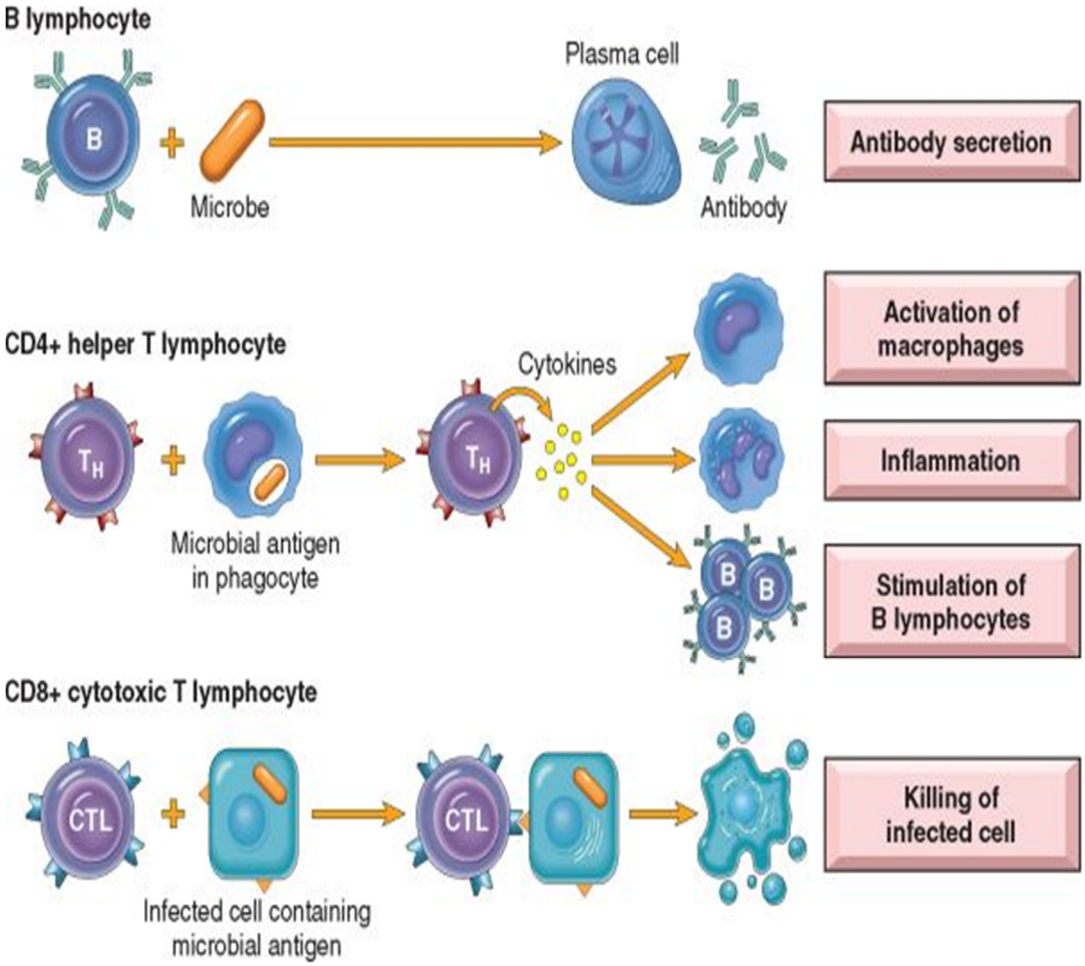


## ACQUIRED IMMUNITY

Consists of humoral and cell mediated immunity.

## HUMORAL IMMUNITY

This type of immunity occurs with the help of immunoglobulins or antibodies. B cells are the main cells which are responsible for production of immunoglobulins.



## CYTOTOXIC IMMUNITY

Mainly caused by the T cells which are of the following type:

i. T helper cells

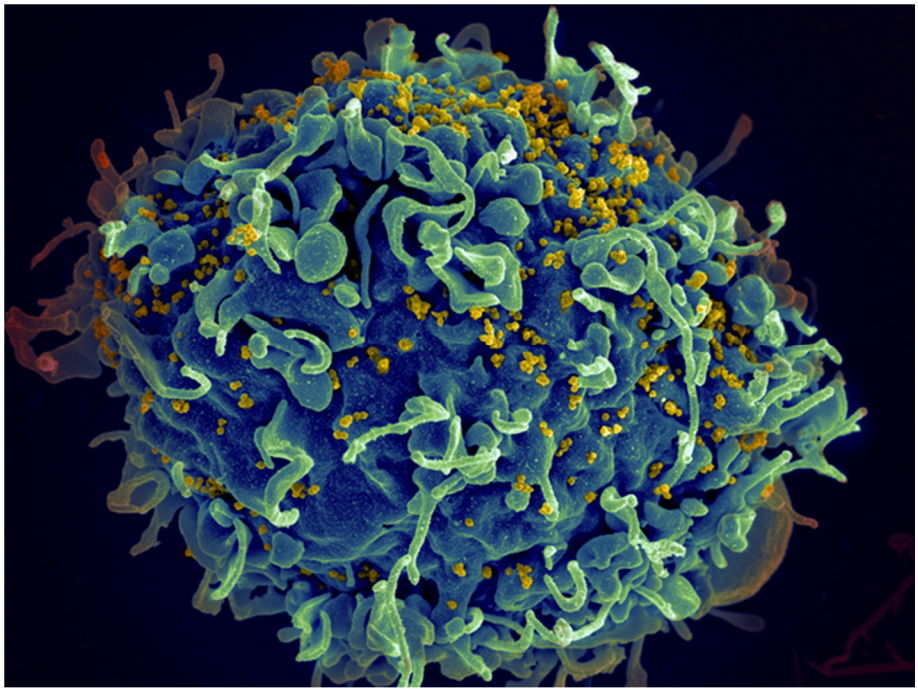
ii. Cytotoxic T cells

iii. Regulatory T cells

iv. Memory T cells

## HELPER T CELLS

They release cytokines to the blood stream that cause the activation of immune system against the impending danger to the body.

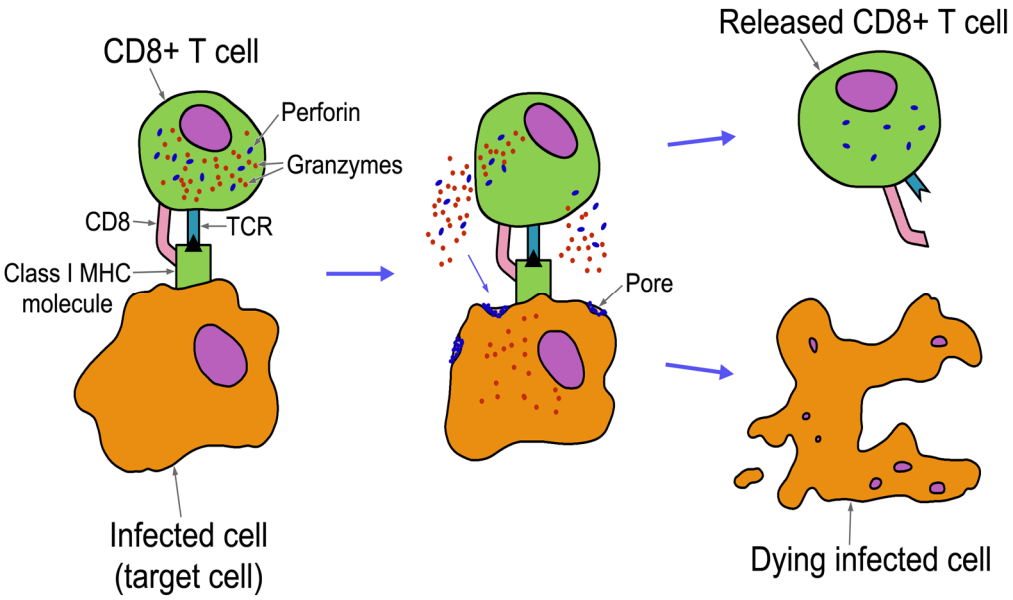


**Helper T cell**

## CYTOTOXIC T CELLS

These are also called as CD8 positive cells. When a cytotoxic T cell recognises a cell as pathogenic it will do either of the two things

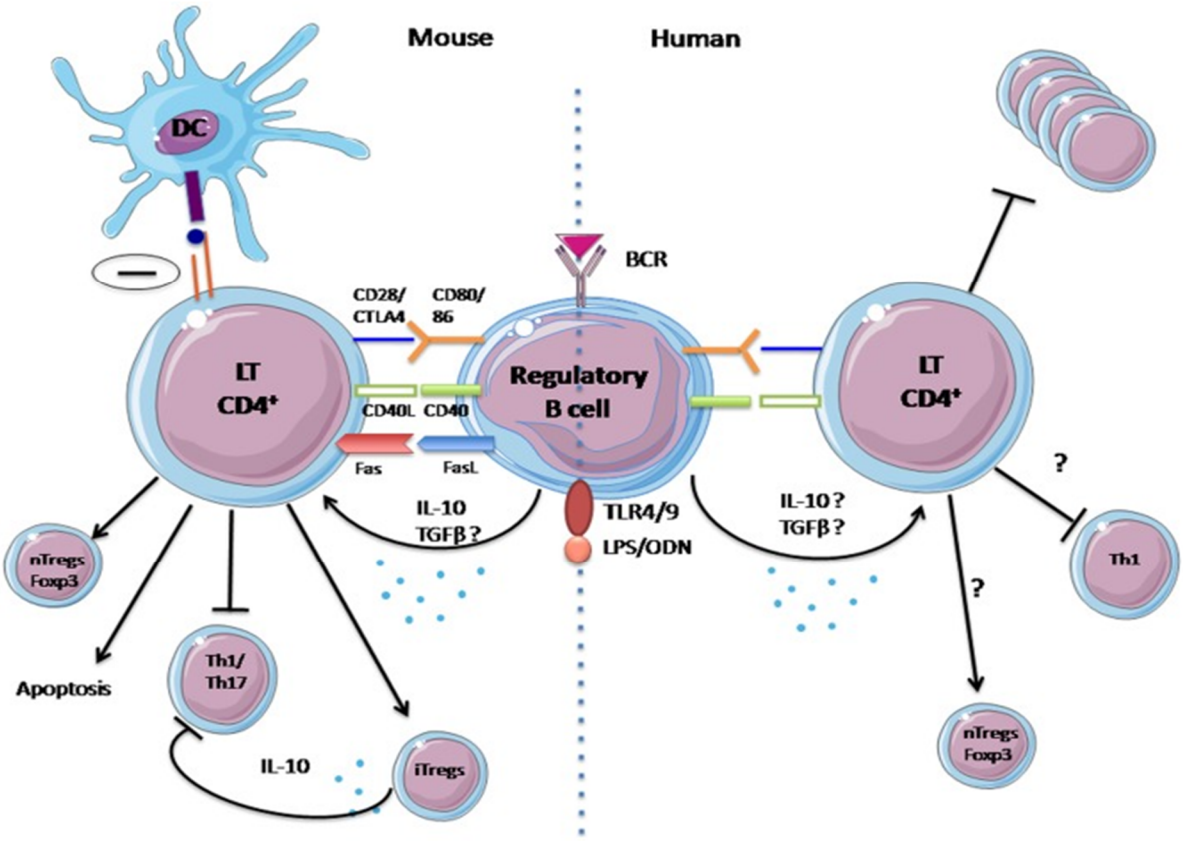
1. Cause apoptosis of the cells
2. Secrete enzymes for the destruction of the cell.




**TCR – T Cell Receptor**

## REGULATORY T CELLS

These cells mainly depend on the major histocompatibility recognising a cell as a host cell or not thereby regulating their activation or suppression [11].



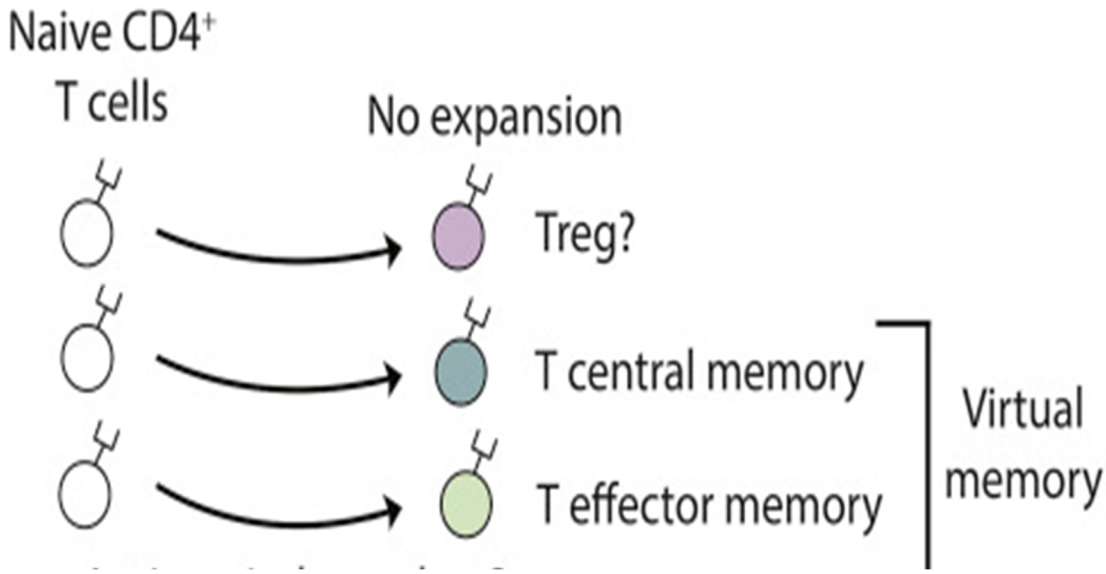

**IL – Interleukin, TGF – Transforming growth factor, IFN – Interferon, BCR – B Cell Receptor**

**Regulatory T cell**

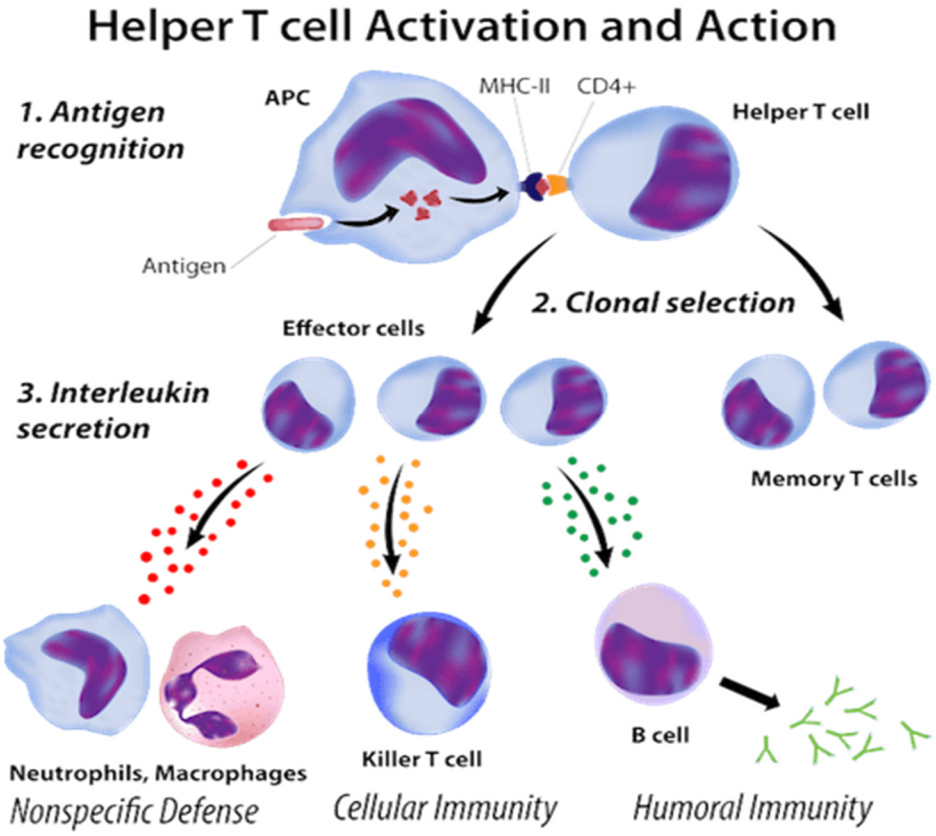
## MEMORY T CELLS

Some of the T cells get converted into memory cells so that the same antigen can be identified in the future and thereby can be dealt rapidly when they come in contact in the future.

Mainly by the help of T cells, these are targeted to destroy a particular cell and act specifically.




**Activation of Memory T cells**




**APC – Antigen Presenting Cell, MHC – Major Histocompatibility**

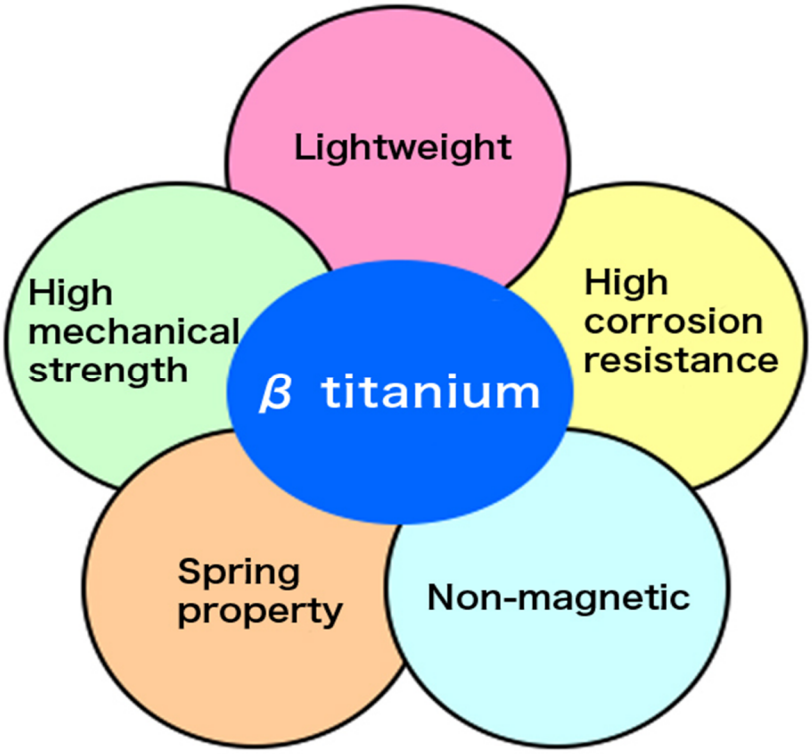
## TITANIUM

Titanium is a transition metal which was initially discovered in the year 1791 by William Gregor [12]. It constitutes of 0.6% of earth crest.

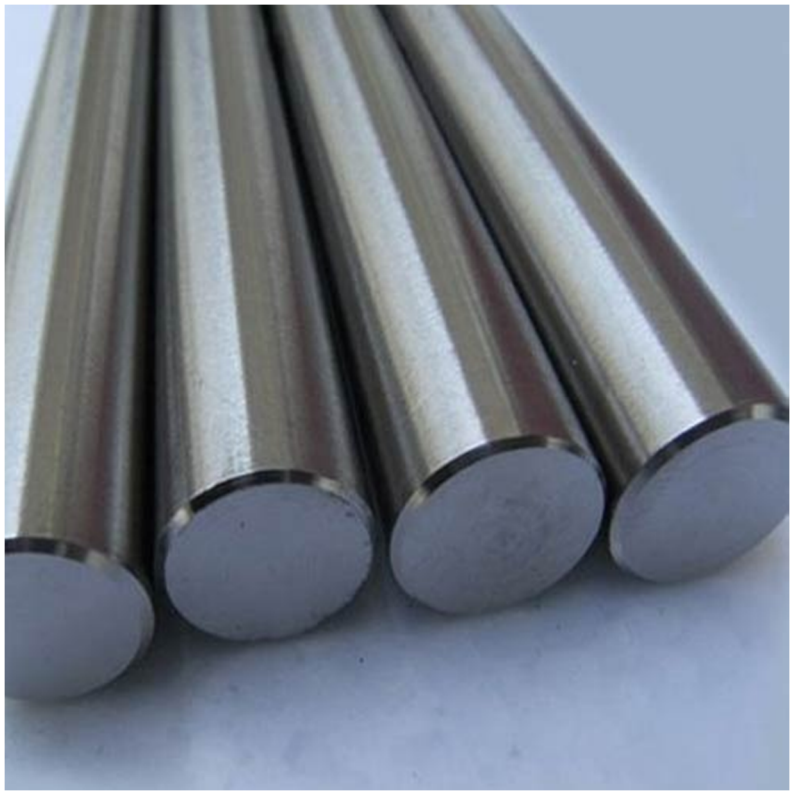
It is metallic silver in colour. It is solid at room temperature and the strength of titanium drops to 50% if the temperature is increased for about 200 degree centigrade. It weighs lighter than other metals and can with stand certain amount of corrosion and a reasonably high amount of heat.

The main source of titanium extraction is from rutile. The titanium during its extraction process is converted to titanium dioxide which is a more resistant form

Its various uses are in medical field mainly for the manufacture of metal implants as it is considered as physiologically inert, it is also used in manufacture of aircrafts, naval ships, space crafts , missile also in stainless steel to reduce carbon content, in steel alloys to reduce grain size and as a deoxidiser.




**Properties of Titanium**

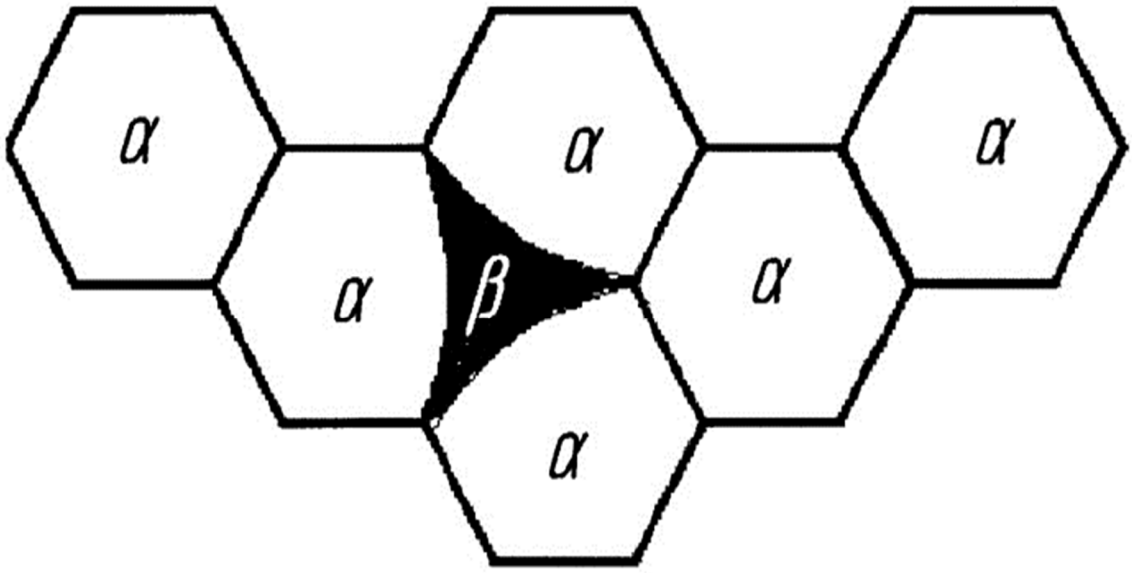


**Titanium alloy which are manufactured and stored as rods**

## TITANIUM ALLOYS

Alloys are being prepared in combination with alluminium, gadolinium etc, all these are alpha stabilisers because they increase the transformation temperature of alpha to beta forms.

Molybdenum, Vanadium are the beta stabilisers as they lower the transformation temperature. Manganese, chromium and ferrum on addition produce a eutectic reaction thereby decreasing the temperature at which the transformation occurs [13].




**Alpha and beta structural arrangement of titanium**

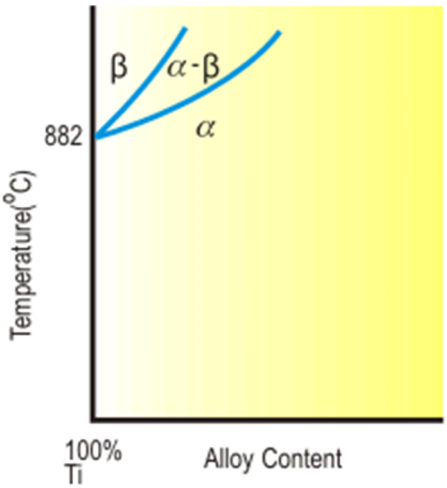
Molybdenum and vanadium are the two metals which have their greatest influence on the beta stability so they are used as the most common alloying agents. One more metal that is added to it is tungsten due to its high density.

Copper is added to make the alloy still more hard so that it can withstand heat to a certain extent. Copper is added in an amount of less than 2.5% of the weight in the commercial alloys.

Titanium has the capacity to absorb around 60% of hydrogen. This can be removed if needed with the help of the process called as annealing in a vaccum so that it can have properties like high stength and good ductility.

**Specific alloys**

Niobium is added to titanium to make it resistant to oxidation.




**Tranformation between the two forms in relation to heat**

Carbon is added to titanium to allow a greater temperature range in which it can be in both alpha and beta form and to help in thermo mechanical processing.

Alluminium helps to reduce the density,strengthens the alloy and also stabilises the alpha form. Vanadium addition provides a greater amount of ductility to the alloy.

Chromium addition to the alloy in range of 10% of the weight helps to increase the burn resistance.

## CORROSION OF METALS

It is the degradation of the metal due to some chemical reaction with the environment that is invitro or invivo mainly due to oxidation process

## TYPES OF CORROSION

i. Intergranular corrosion

ii. Pitting

iii. Fretting

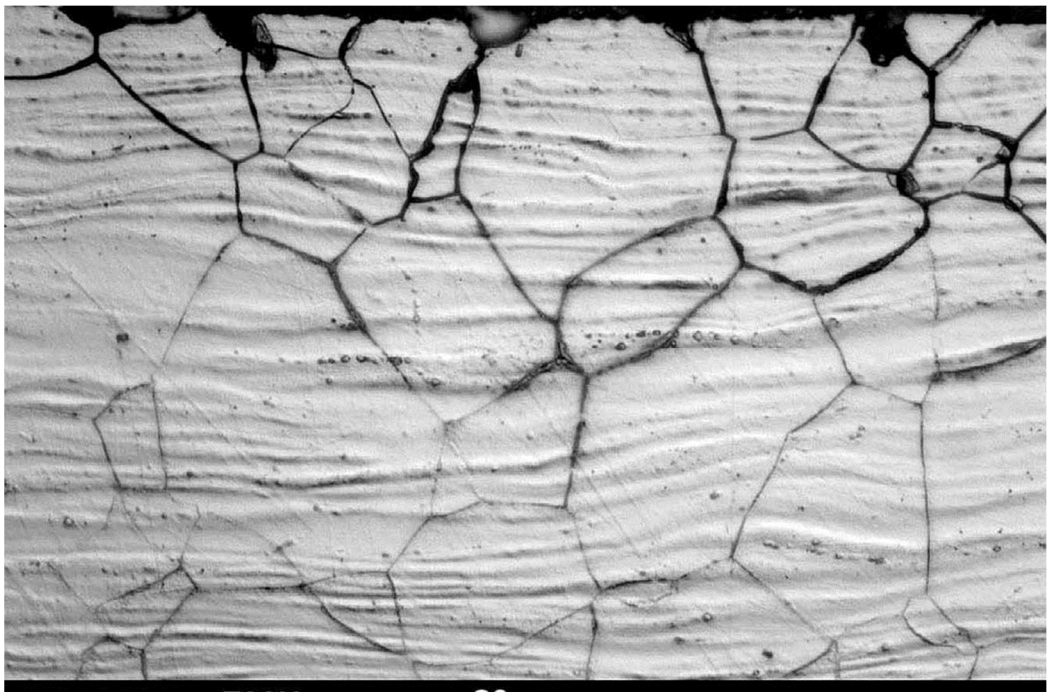
iv. Galvanic corrosion

v. Stress crack corrosion

vi. Crevice corrosion

**Intergranular Corrosion** – It is a type of surface corrosion where in the erosion occurs near the grain boundaries in the metal. Whenever there is composition difference grain boundaries become highly reactive. The alloy loses its strength due to grain fallout due to corrosion.

Intergranular corrosion is more common in nickel based alloys, stainless steel and also aluminium mixed alloys. It is when the carbon content of austentitic stainless steel is below 0.03% carbide reproducibility reducing the risk of corrosion [14]. To avoid this kind of corrosion carbon content of the surgical equipments to be reduced.

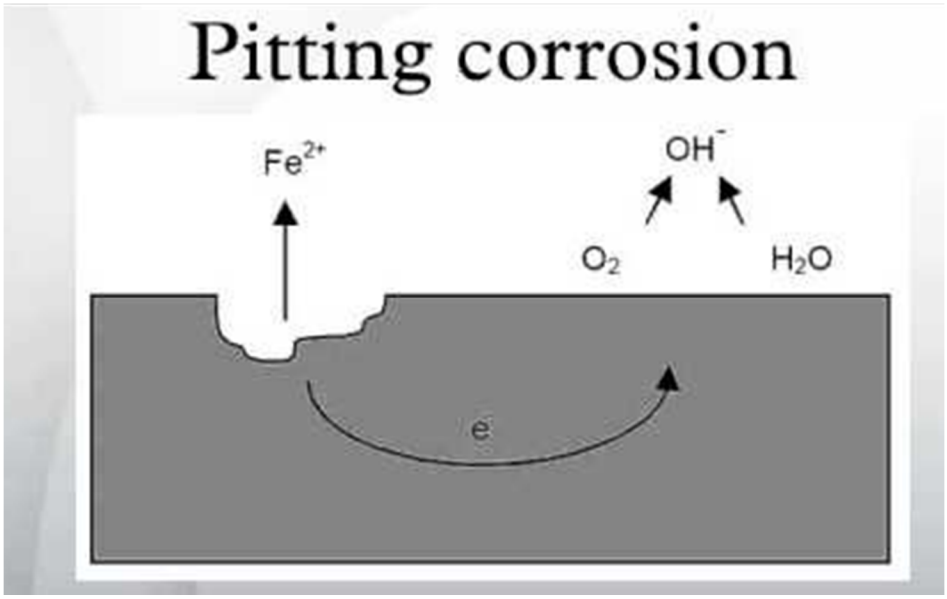


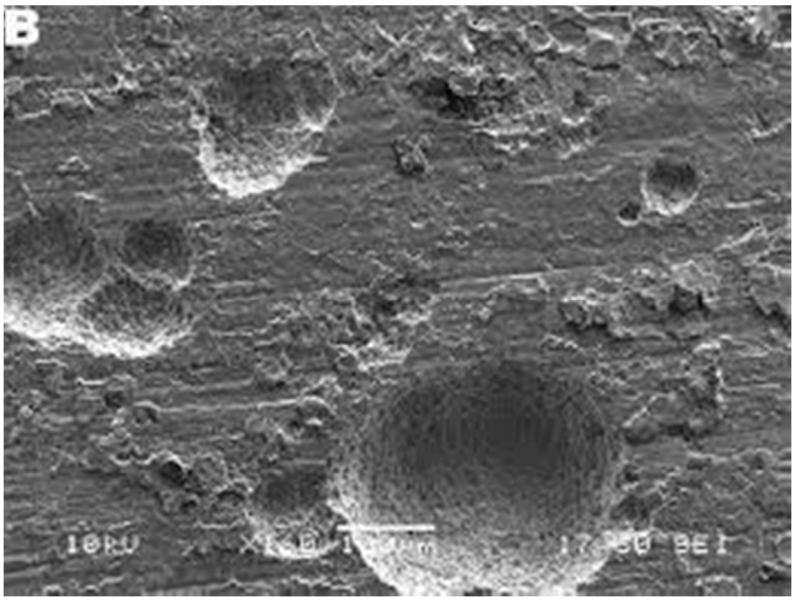
**Microscopic structure of intergranular corrosion**

**Macroscopic structure of interganular corrosion**

## PITTING

It occurs due to the degradation of the oxide film and is a type of local corrosion. There will be formation of cavities on the surface of metal. It is one of the most common type of corrosion [14] and it is autocatalytic in nature.

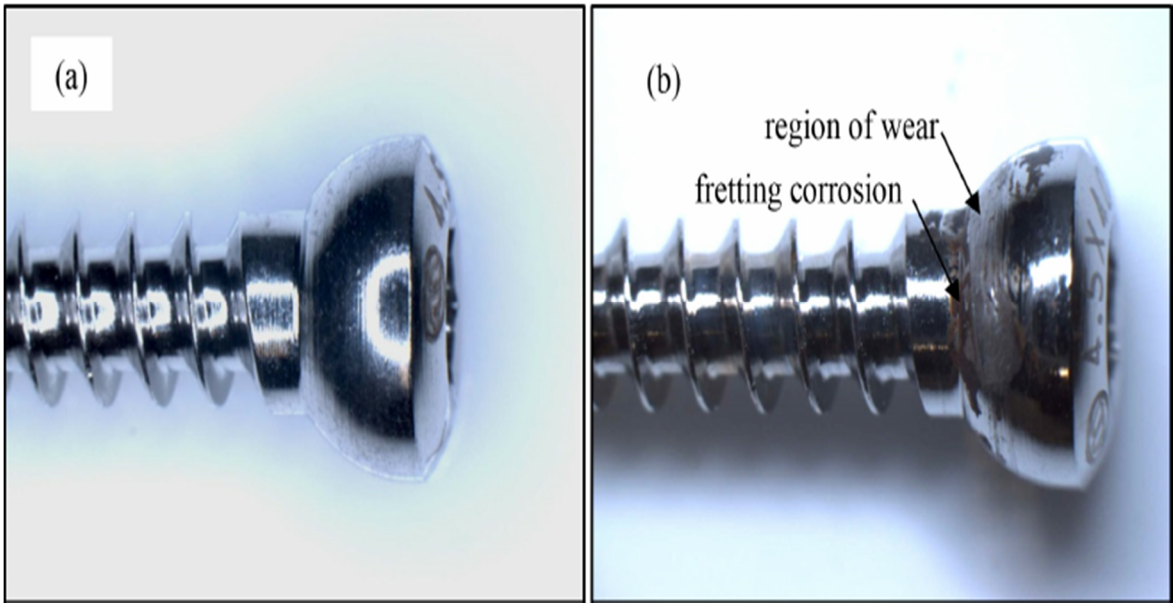


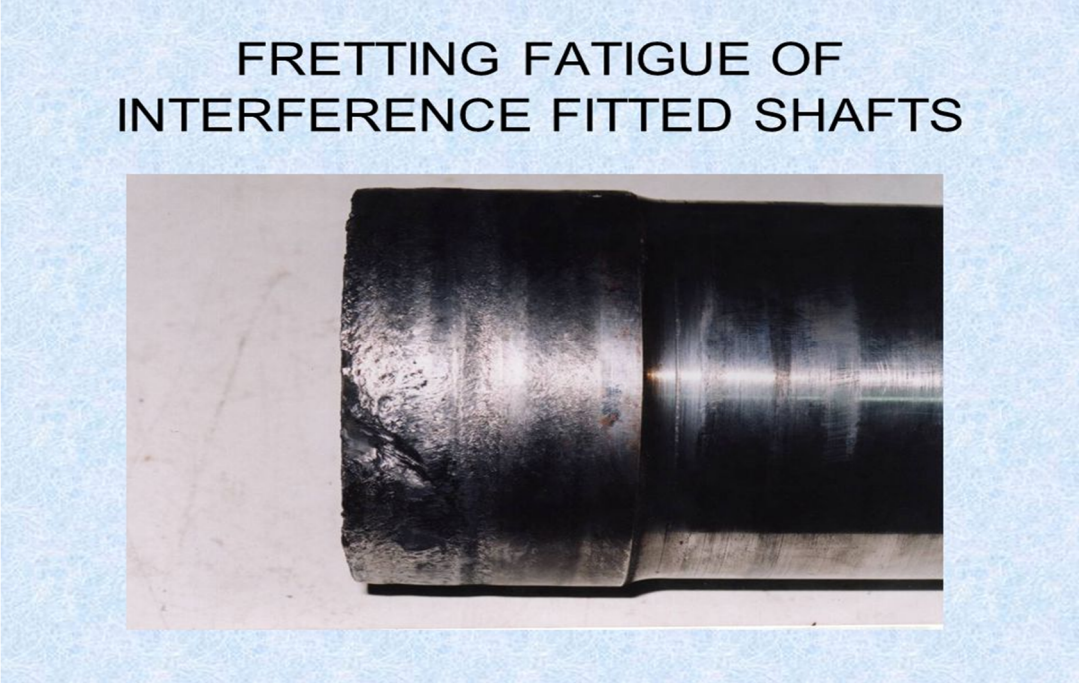

**Pitting corrosion over a metallic surface microscopic view**

## FRETTING CORROSION

This is a type of damage to the surface of the metal caused under load and in the presence of frequent movement or friction over the surface. Usually occurs at the area of contact of two metal surfaces. The degradation products due to fretting of implants immersed in extracellular fluid is usually oxides containing the chromic chloride and occasionally potassium dichromate. The surrounding fluid may also contain calcium, nickel, chloride due to degradation process.




**a , b - Fretting corrosion of screws in an implant**

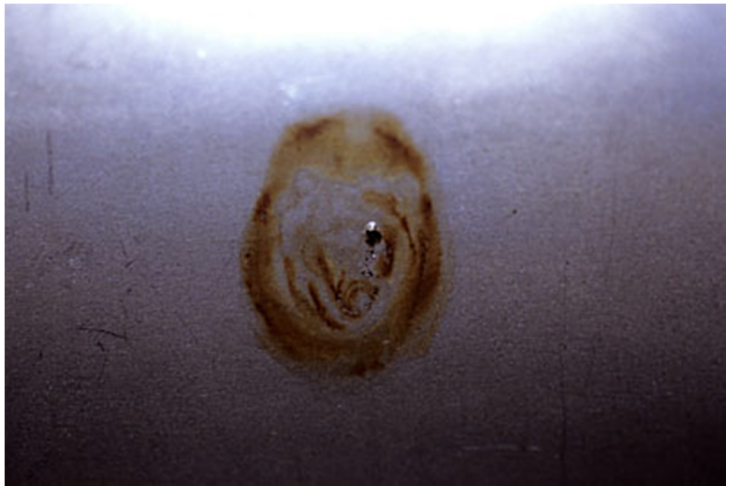



**Contact area of two metals under load**

## CREVICE CORROSION

It is also a form of localised corrosion which occurs at the sites like welded, bolted or riveting area where there will be crevices which are difficult for the aqueous solution to reach which covers rest of the metal surface. It is also known as deposit attack [15]. These areas which are difficult to access gradually degrade due to lack of the antioxidant coat present elsewhere in the surface of metal.

**Crevice corrosion**



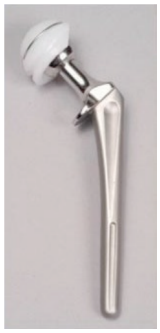
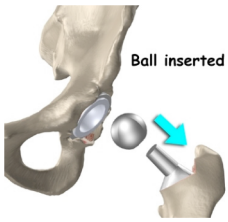
**Crevice corrosion at the overlapping surface**

## GALVANIC CORROSION

In this type of corrosion there will be two dissimilar types of metals which will be in contact with a conducting fluid surrounding it. Here any one of the two metal will start corroding and the other metal will be protected against corrosion. This type of corrosion usually does not depend on type or texture of the metal. The zone affected is the shiner

aspect of the metal. The characteristic of corrosion is not generalised unlike in intergranular but highly local .

**Galvanic corrosion**

| Types of corrosion | Material | Implant location | Shape of the implant |
|---|---|---|---|
| Pitting | 304 SS, Cobalt based alloy | Hip |  |
| Crevice | 316 L stainless steel | Bone plate and screws |  |
| Corrosion fatigue | 316 SS,<br>CoCrNi | Bone cement |  |
| Fretting | Ti6Al4V, CoCr | Metal on metal |  |
| Galvanic [16] | 304SS/316SS,<br>CoCr+Ti6Al4V,<br>316SS/Ti6Al4V | Screws and nuts |  |

## CORROSION OF METAL IN THE BODY

In the field of biomaterials the most important criteria is the acceptability of material by the body without causing toxicity or hypersensitivity reaction or any other systemic reactions in the host.

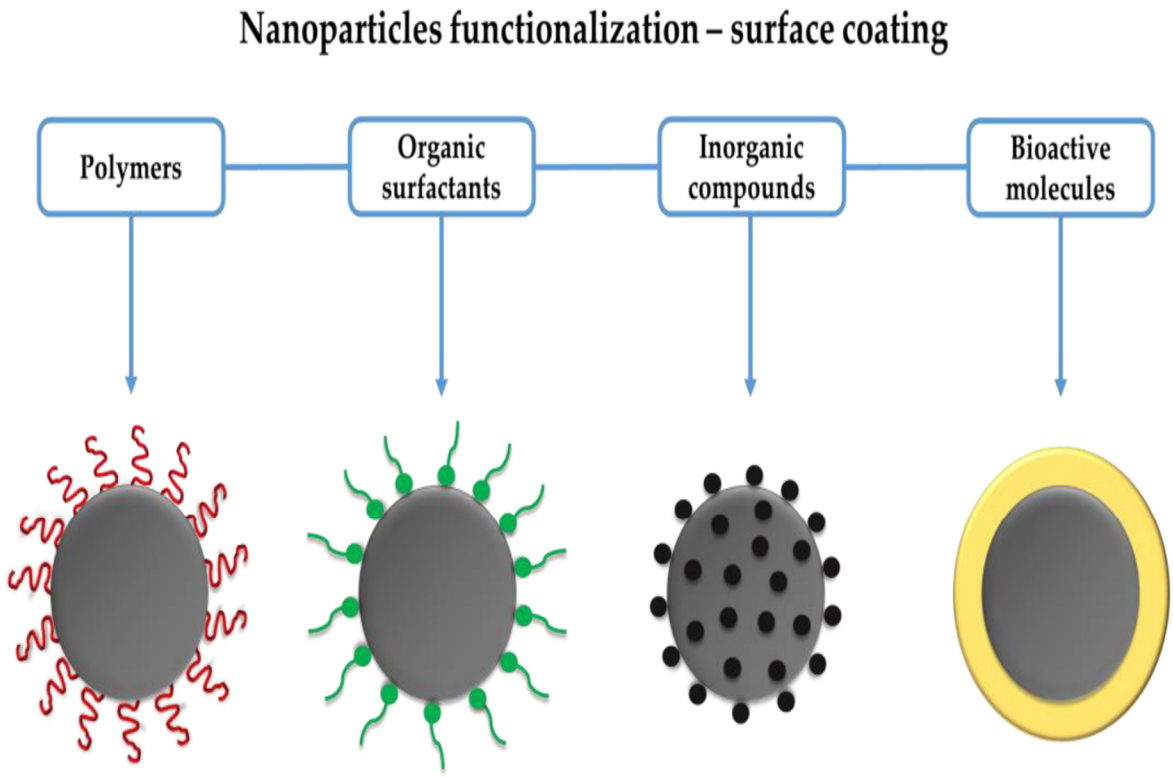
The next thing is the strength of the material as it has to act as a supporting structure for the deficient structural support, one more important feature that should be considered is its resistance to corrosion, fatigue resistance in various environment invivo.

Implants are exposed to various types of corrosion environment like blood, saliva which has several constituents like plasma, chlorine, amino acids, sodium. The fluid medium in the body contains various ions like potassium, calcium, magnesium, sodium etc. Proteins which are present in the surrounding environment can bind to the metal ions present on the surface of the implant and can carry them to various other parts. In addition the proteins that are absorbed on the surface of the implant can reduce the diffusion of oxygen and this may lead to corrosion over the surface.

Cathodic reaction leads to formation of ions like hydrogen which inhibit corrosion but if the environment has the presence of

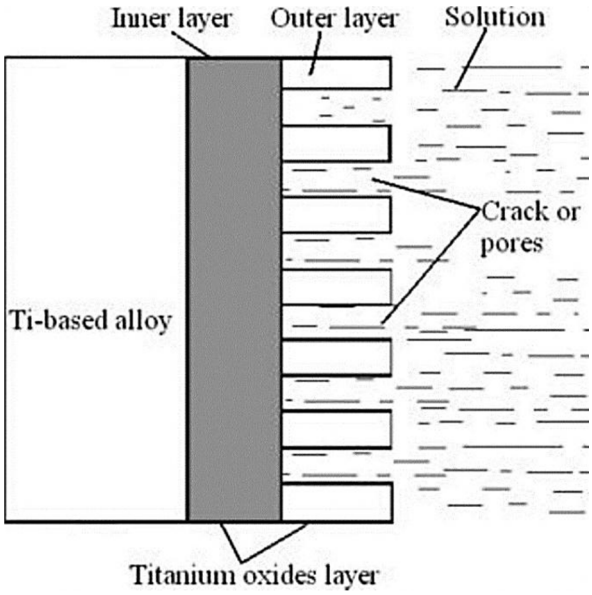
microrganisms like bacteria then these absorb the hydrogen ion thereby breaking the barrier and causing corrosion of the implants.

Two main physical factors that determine corrosion of the implant surface are thermodynamic forces and the kinetic barrier. Thermodynamic forces cause corrosion by reactions such as oxidation or reduction whereas kinetic barrier by surface oxidation layer.

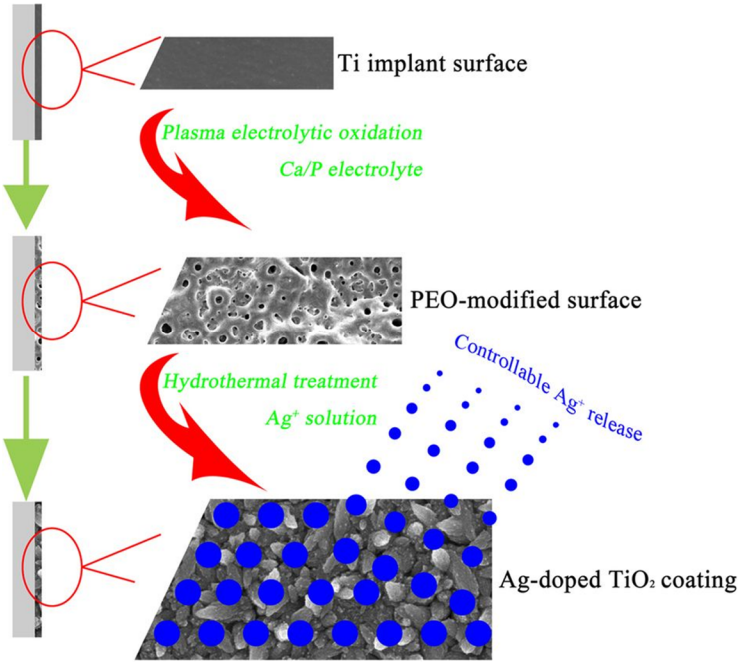



Corrosion such as fretting leads to loss of surface protective oxide layer. That leads to crack and crevices which forms a catalytic site for the formation of corrosion inducing reactions. So to prevent the corrosion the initially formed oxide layer should be non-porous, highly resistant to

abrasion and also an atomic structure that will decrease the binding of proteins or other migration of ions.




**Cracks or pores causing damage and leading to corrosion**




**PEO – Polyethylene Oxide**

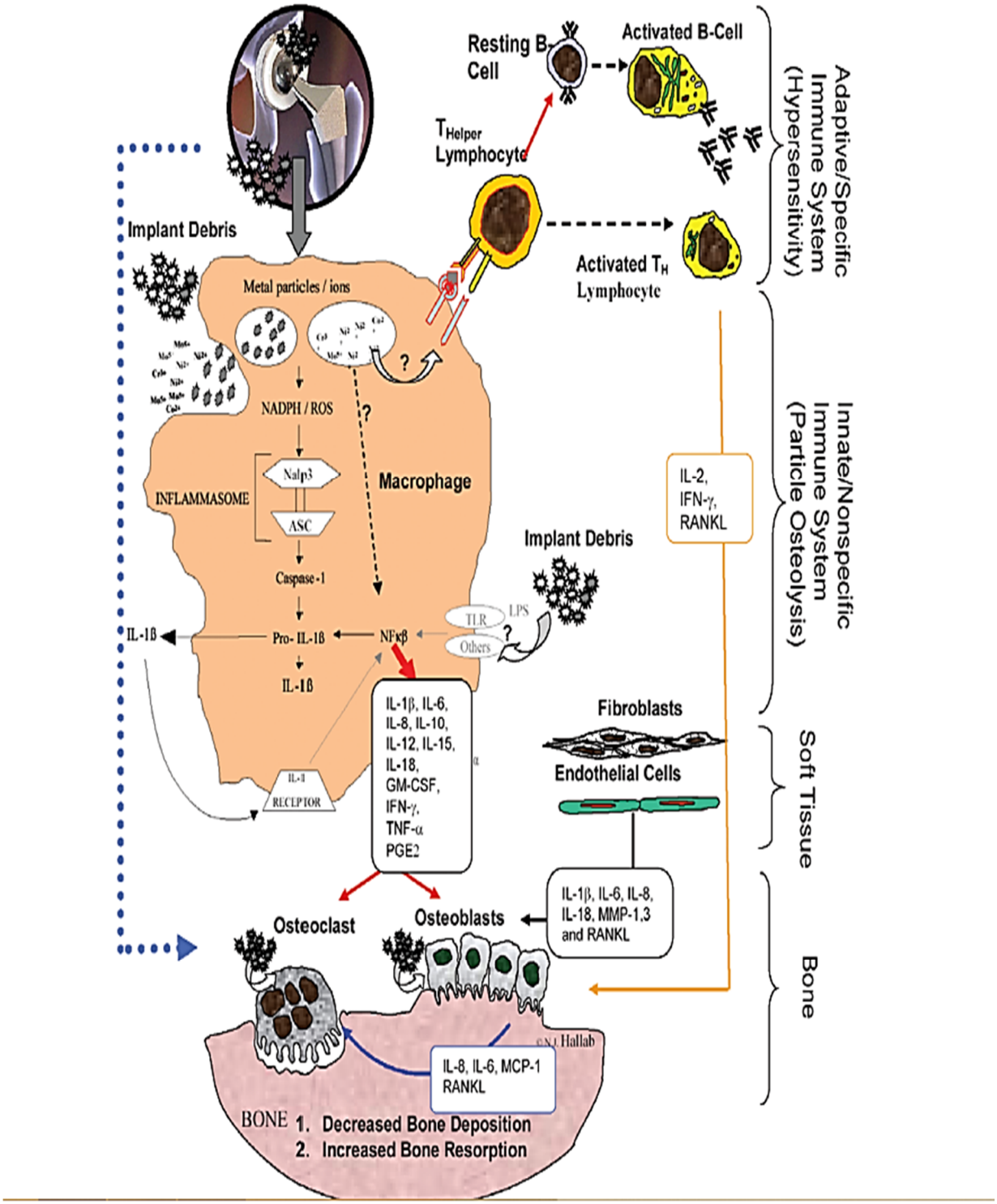
**Titanium alloy coated with oxidised layer (titanium dioxide)**

## CYTOKINES IN CORROSION

Cytokines are the low molecular weight protein molecules. These are released at the local site by the immune system targeting the bacterial or other foreign cells. Implant some time may be exposed to the cytokines leading to damage of the oxide layer thereby leaving it amenable for corrosion.

## IMPLANT AND SURROUNDING TISSUES

The surrounding tissues in an implant which has started corroding will contain the maximum amount of the implant material and there will be discolouration of the tissues due to reaction with the body fluids and the implant surface. During surgery a sample of the local tissue can be sent for the analysis to confirm thereby hypersensitivity or metal toxicity can be handled carefully.




**IL – Interleukin, IFN – Interferon, MMP – Matrix metaloproteinase,**

**MCP – Monocyte Chemo attractant protein**

**Pathophysiology of Implant Corrosion**

# MATERIALS AND METHODOLOGY

A prospective study of "Serum titanium estimation in postoperative individuals with titanium implant using inductively coupled plasma mass spectrometry and its clinical correlation" was conducted in Coimbatore Medical college and hospital.

The present study is conducted on 25 patients who had titanium implant in their body for some orthopaedic procedure during the year May 2016 to September 2018.

After obtaining clearance and approval from Institutional Ethical Committee and patient fulfilling inclusion and exclusion criteria were included in the study after Informed Consent.

Study design: Prospective study

Duration after which blood sample collected: 6 months.

**INCLUSION CRITERIA:**

- Patients who have undergone orthopaedic procedure with titanium implant in Coimbatore medical college and hospital between 2016-2018
- Age group between 5-75yr.

**EXCLUSION CRITERIA:**

- Patients who already has some other metallic implant in his body.
- Implant which has been removed recently.
- Patient who is a known case of chronic renal or hepatic disease.

**PARAMETERS THAT WERE LOOKED FOR JUDGING THE TOXICITY**:

- Complete haemogram.
- Renal function parameters.
- Liver function parameters.

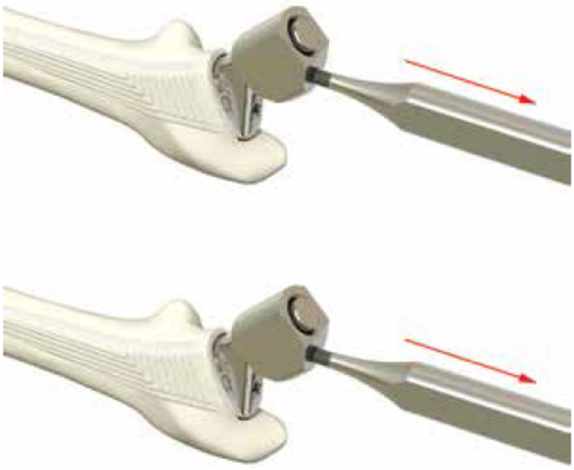
Various implants whose blood toxicity levels studied in this study are:

- Acetabular component reflection 3/no hole with **Co-Cr**
- **Ti6Al4V ISO 5832-3** polar stem (femoral component)

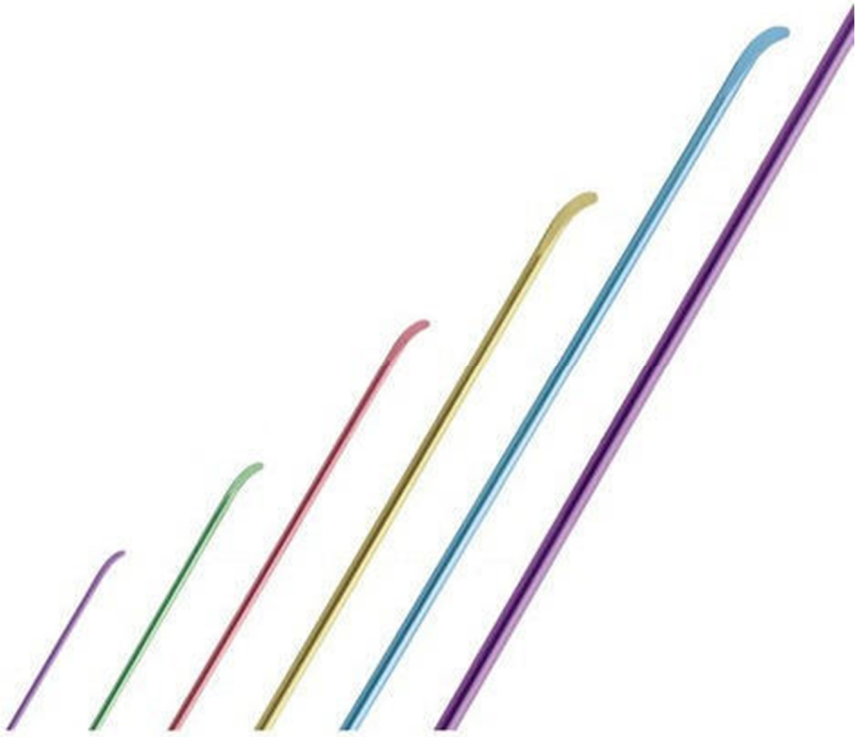
**Acetabular Components offer the option of peg fixation**

**All the screws are 6.5mm cancellous screws with a 4.0mm minor diameter**

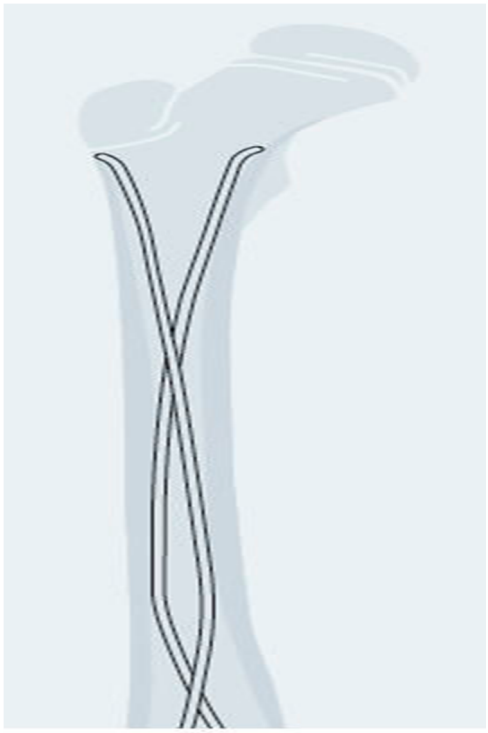
**Ti6Al4V ISO 5832-3 polar stem (femoral component)**



# TENS NAIL



**Various sizes of tens nail**



**PROCEDURE**

After a duration of 6 months of implanting a titanium implant 4 ml of blood is drawn using sterile disposable syringe with a needle by using S monovette method.

**Sterile disposable syringe with the needle**

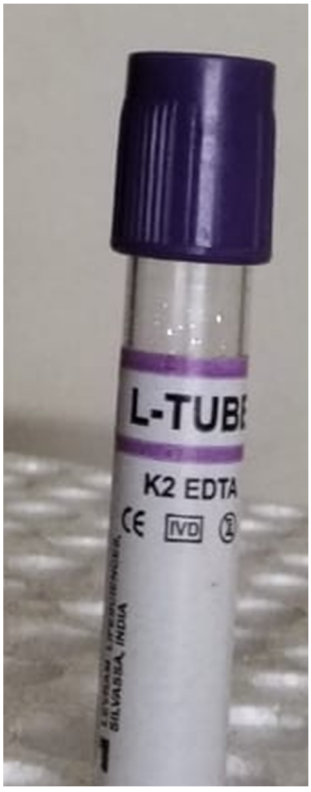
## METHOD FOR BLOOD COLLECTION

Forearm veins is most commonly used to draw the blood in this study. Initially patient in a comfortable lying position tourniquet is applied to the arm. The puncture area over the skin is sterilised with the help of isopropyl alcohol in a cotton swab.

Patient is advised to do repeated fisting and unfisting so as to make the vein more prominent. Properly visualise and palpate the vein. Needle with the bevelled side facing up the vein is punctured and made sure that its not entering the other side of the vein. Blood is drawn by s monovette method that is by the help of the vacuum blood is allowed to collect by itself.

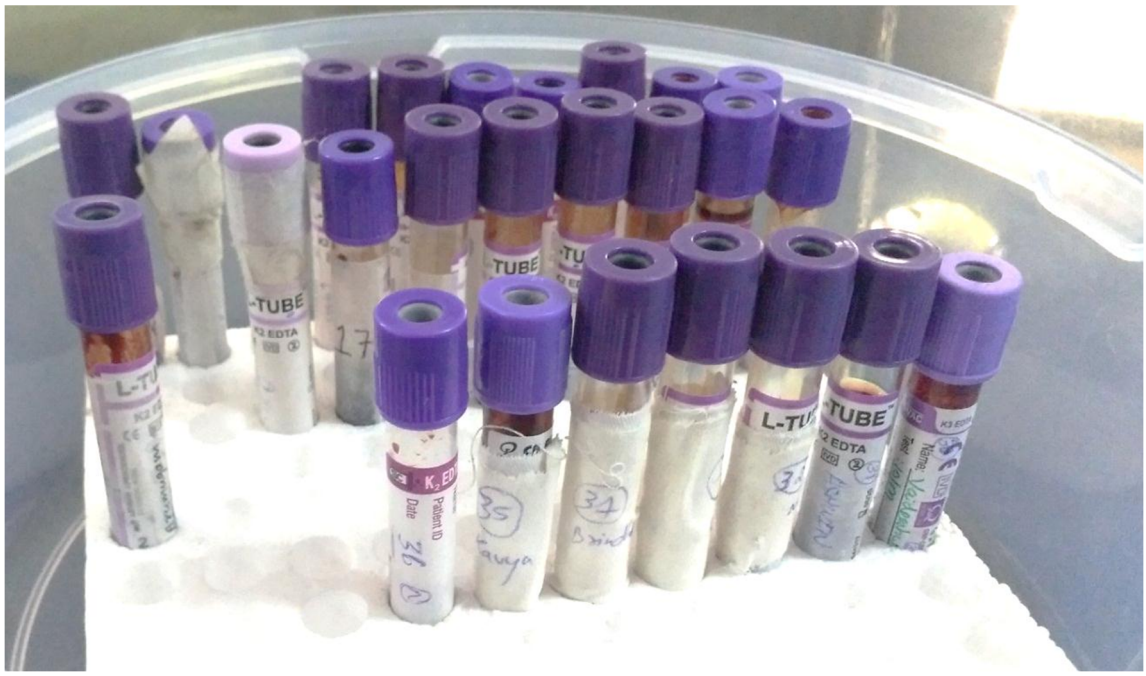
When sufficient quantity of blood is collected the needle is withdrawn gently. With a help of guaze piece sustained pressure is applied over the area for around 3-5 minutes until further oozing of blood stops. A sterile plaster is applied over the area.

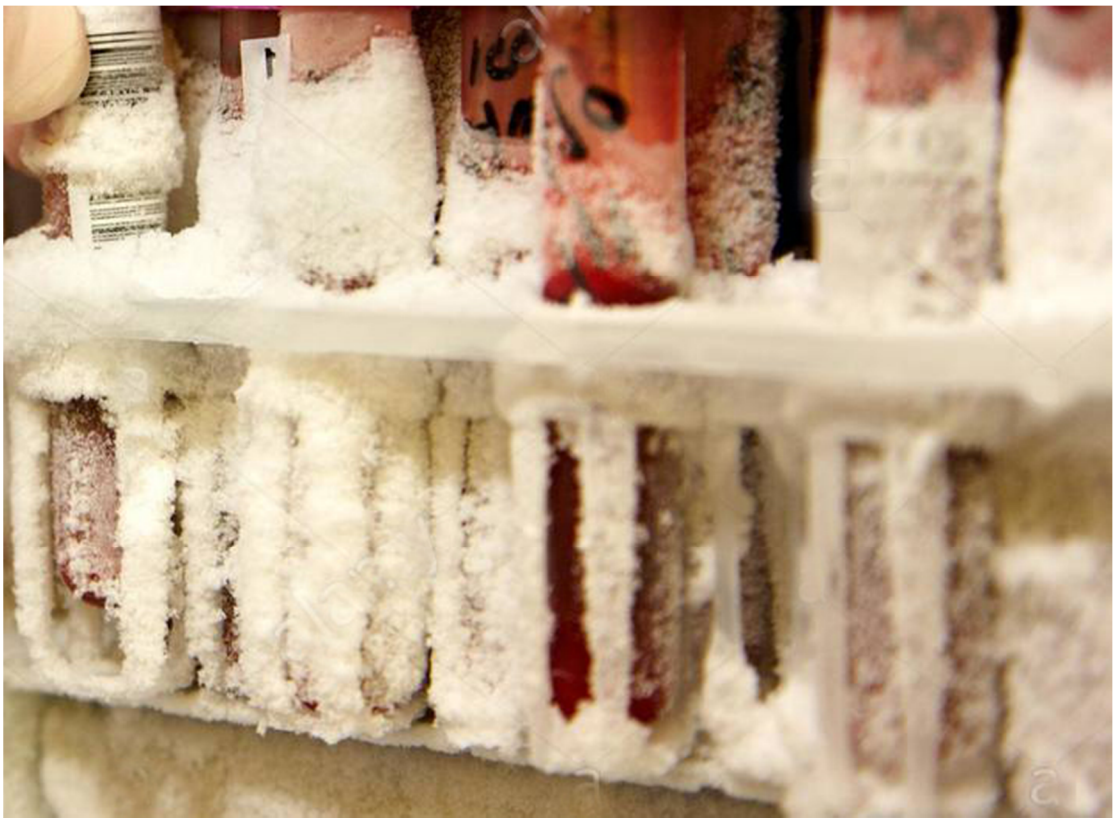
The blood drawn is transferred to a vacutainer containing K2 EDTA (Ethylene diamine tetracetic acid) solution and mixed well.




**Vacutainer**

**Samples collected labelled and stored**



**Cold Storage**

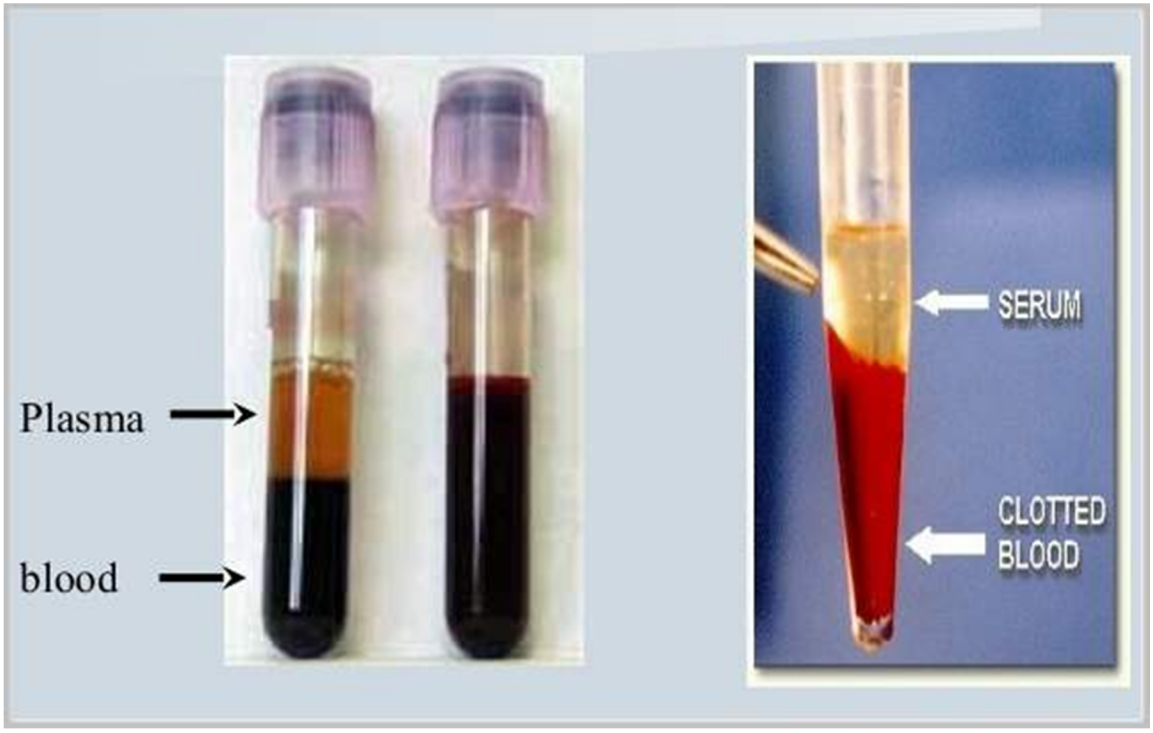
**Cold storage compartment**

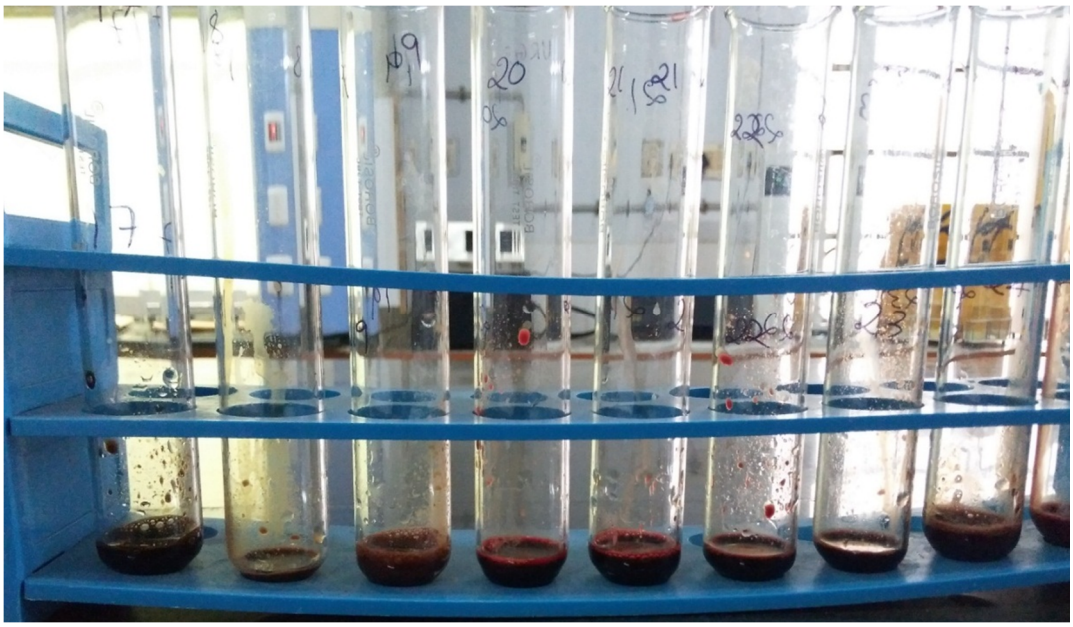
- The samples collected are stored in cold storage at -10 degree celsius.
- The samples are then subjected to centrifugation at 4000 rpm for about 20 minutes.
- After the centrifugation the serum is collected by using a pipette with a sterile disposable plastic tips and transferred to borosil test tubes.
- Borosil test tubes are highly resistant to heat, acid and other chemicals it also has least levels of heavy metal contamination.


**Centrifugation machine**

**Centrifuging sample**

**Centrifuged sample**



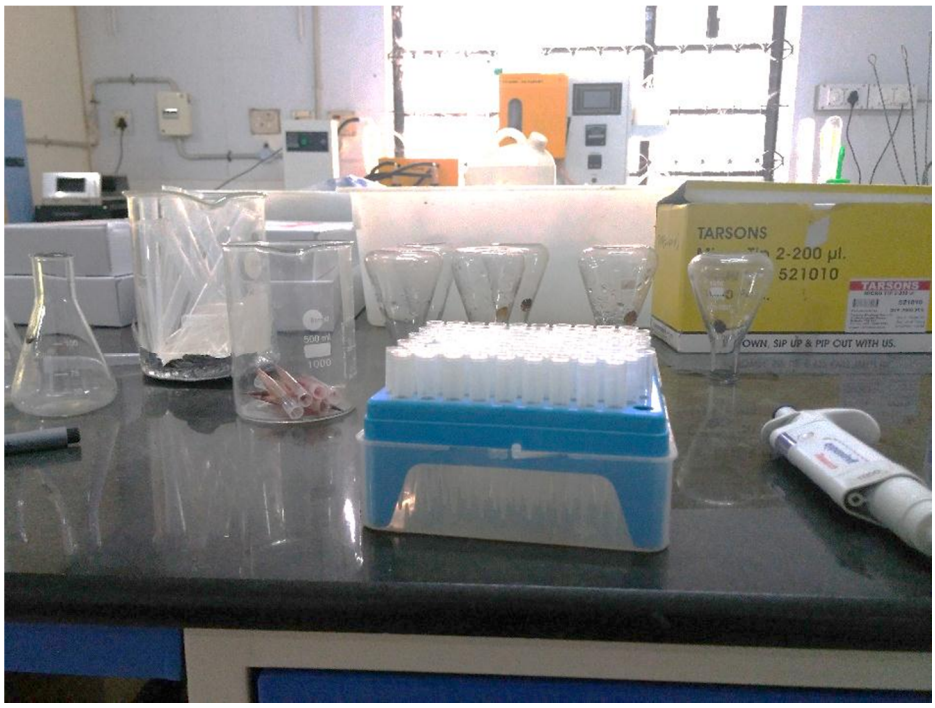


**After centrifugation and separation of the serum**

- 2ml of the supernatant fluid collected after the centrifugation in a test tube is now subjected to triple acid digestion in the following ratio:

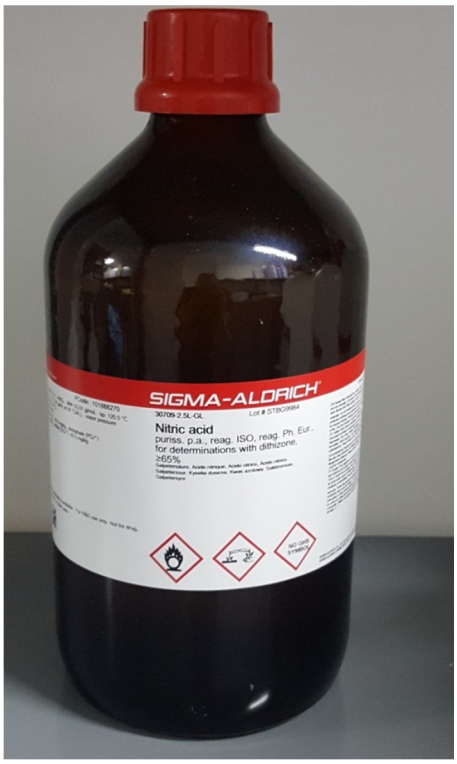
  Nitric acid : sulphuric acid : perchloric acid = **9 : 2 : 1**

- Nitric acid has 60% corrosive capacity
- Sulphuric acid has 80% corrosive capacity
- If only the above two are mixed it is called as diacid digestion where in sulphuric acid to be mixed very slowly to nitric acid but here we add perchloric acid at the end. Perchloric acid has a corrosive capacity of 100%.
- The process of mixing is carried out in the borosil test tubes.
- Now the solution is transferred to broad based beakers.



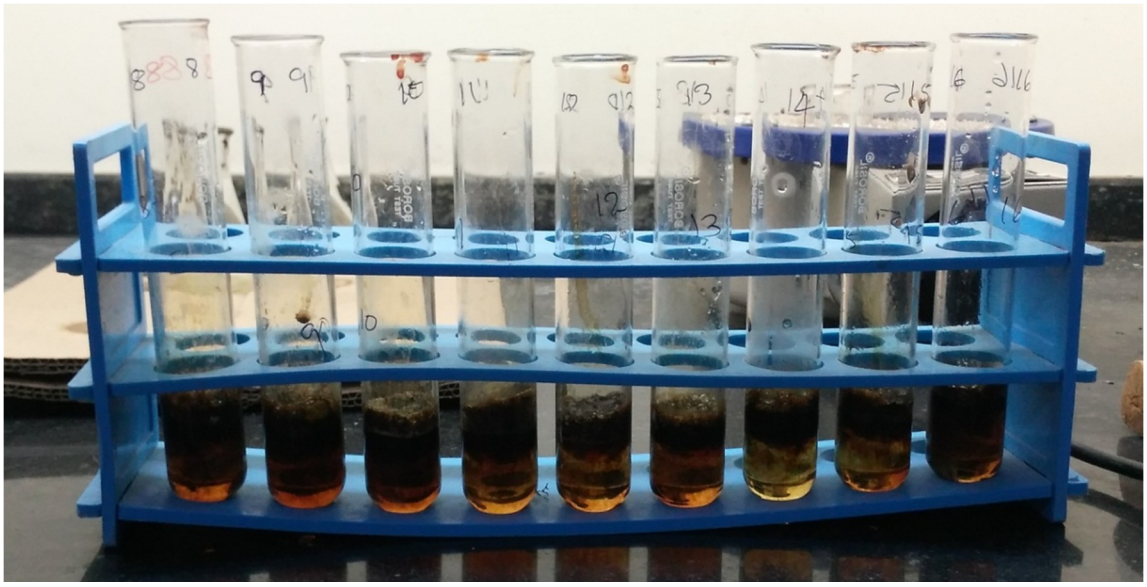

**Disposable Plastic Pippeting Tips**


**Sulphuric acid**




**Nitric acid**


**Perchloric acid**



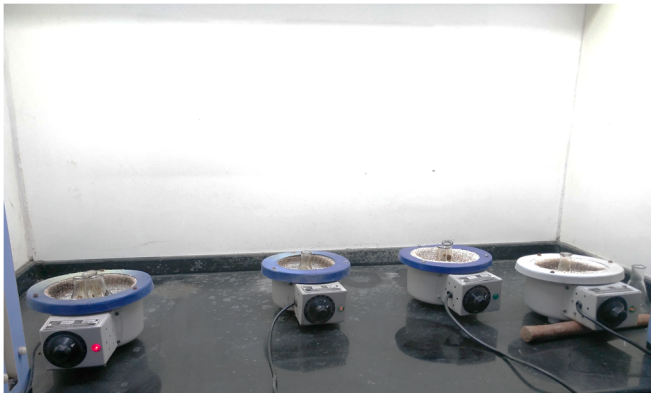
**After triple acid digestion**

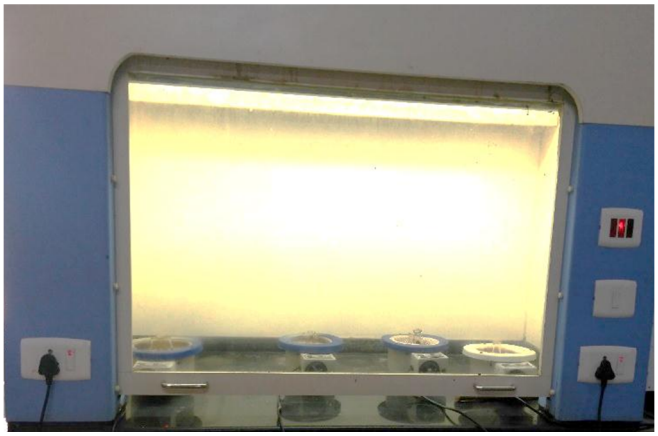
**Broad based beakers with micro pipette tip**

- The samples are now kept in heating mantle and the temperature is set to 80 degree centigrade.
- The heating mantle consists of a jar shaped vessel which is insulated with a porcelain layer.
- The heating chamber is closed as the vapours emitted may cause nasal irritation and breathing difficulty if inhaled.
- The solution is left in the heating mantle until all the liquid present is vaporised.
- It takes around 60 to 80 minutes for the complete evaporation.
- It is confirmed by seeing the test tubes in which we can find the tiny particles attached to the sides of the test tube.


**Equipment to produce distilled water**


**Heating mantle with the solution placed in it.**



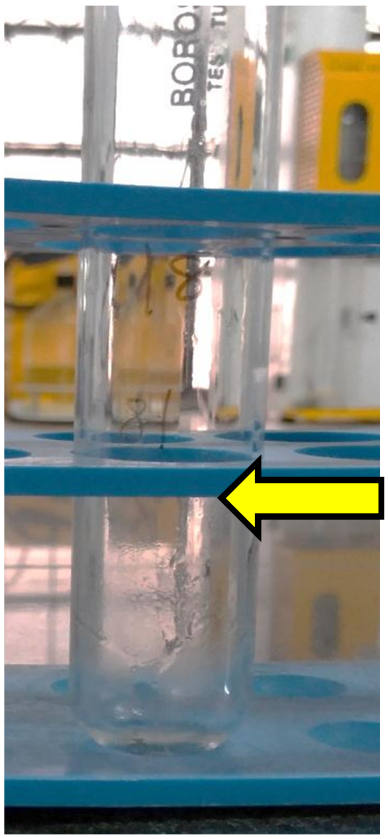


**Heating chamber**

- Now distilled water is added to the test tubes with the help of sterile pipette.
- The particles attached to the sides of the test tube is mixed well using a glass stylus.
- Now the clear solution is transferred into a beaker which has the marking
- The level of the fluid is made upto 10ml

- The whole solution is transferred into a storage vial which is also made up of borosil and then stored.

**After removing from the heating mantle**



**Particles attached to the test tube sides**


**After dissolving in distilled water**


**Storage vials after final process**

- 1ml of each sample is now subjected to **the Inductively coupled plasma mass spectrometry (ICPMS) model NeX Ion 300X,Perkin Elmer, USA**.
- The standard solution was set for measuring titanium levels.
- The results were noted and the same was done for all the 25 samples.
- The results were documented in microgram per litre.


**ICPMS model NeX Ion 300X, Perkin Elmer**

# RESULTS

The results of the study has been tabulated below:

| SI.NO | Titanium (microgram/L) |
|---|---|
| 1. | 1 |
| 2. | 1.02 |
| 3. | 0.16 |
| 4. | 0.89 |
| 5. | 0.4 |
| 6. | 0.3 |
| 7. | 0.27 |
| 8. | 0.2 |
| 9. | 0.11 |
| 10. | 0.29 |
| 11. | 0.13 |
| 12. | 0.42 |

| | |
|---|---|
| 13. | 0.14 |
| 14. | 0.17 |
| 15. | 0.08 |
| 16. | 0.12 |
| 17. | 0.08 |
| 18. | 0.07 |
| 19. | 0.07 |
| 20. | 0.12 |
| 21. | 0.12 |
| 22. | 0.09 |
| 23. | 0.09 |
| 24. | 0.13 |
| 25. | 0.09 |

The range of values are

Maximum: 1.02

microgram/Litre

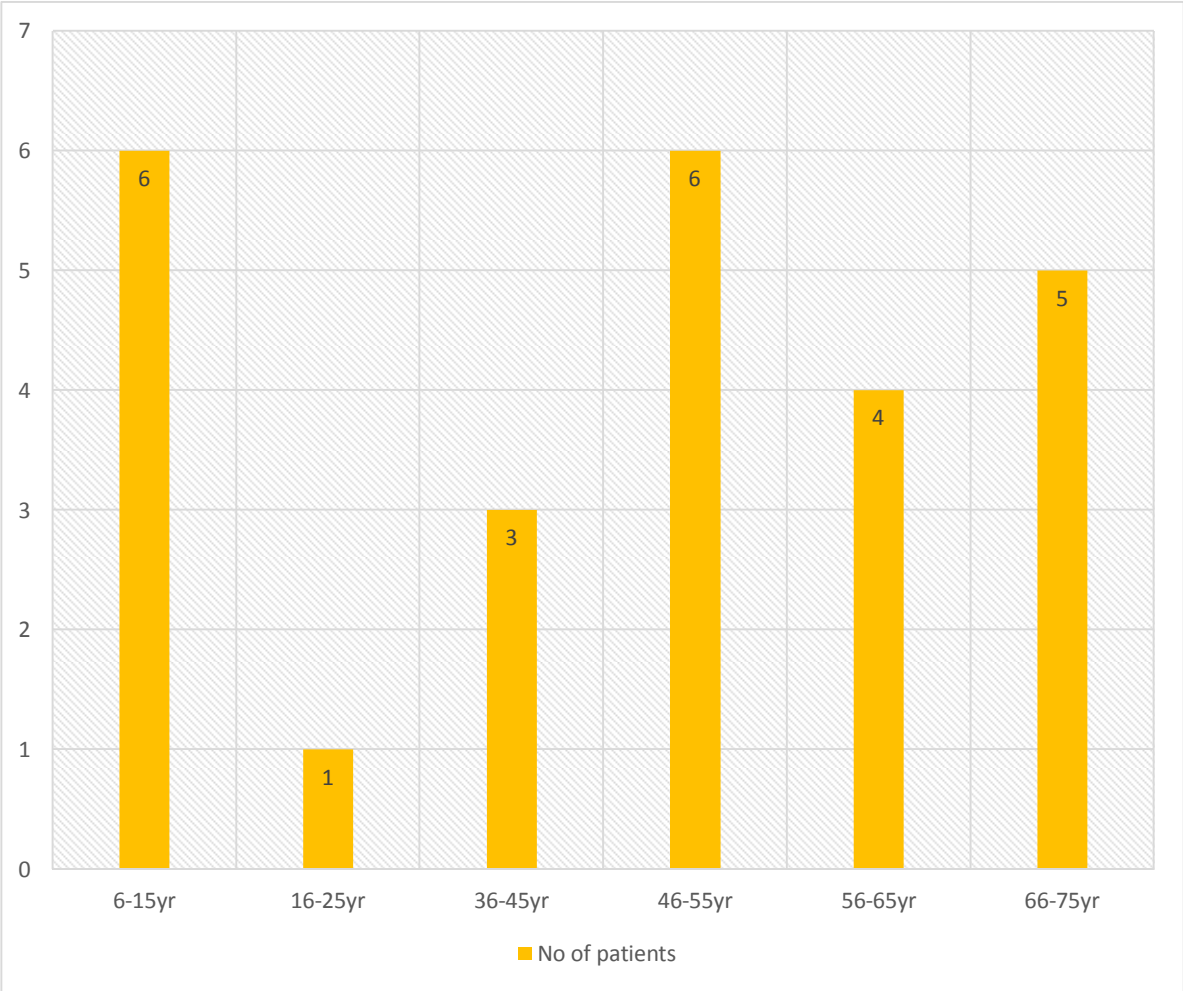
Minimum: 0.07 microgram/Litre

Mean: 0.32 microgram/Litre

**AGE DISTRIBUTION**

| Age group | No of patients |
|---|---|
| 6-15yr | 6 |
| 16-25yr | 1 |
| 36-45 yr | 3 |
| 46-55yr | 6 |
| 56-65yr | 4 |
| 66-75yr | 5 |

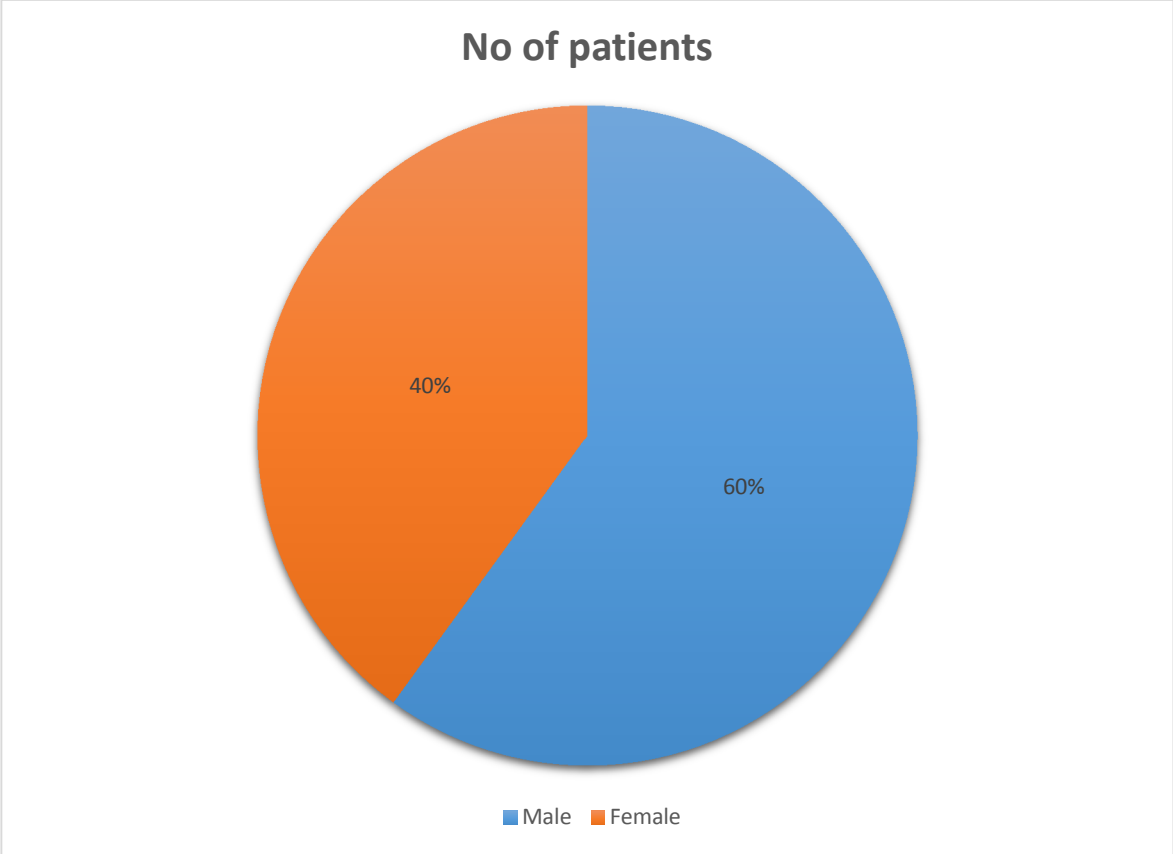
There was no significant difference in serum titanium level in different age group. Majority of the people were in the age group as represented in the graph below:



## SEX DISTRIBUTION

| Gender | No of patients |
|---|---|
| **Male** | **15** |
| **Female** | **10** |

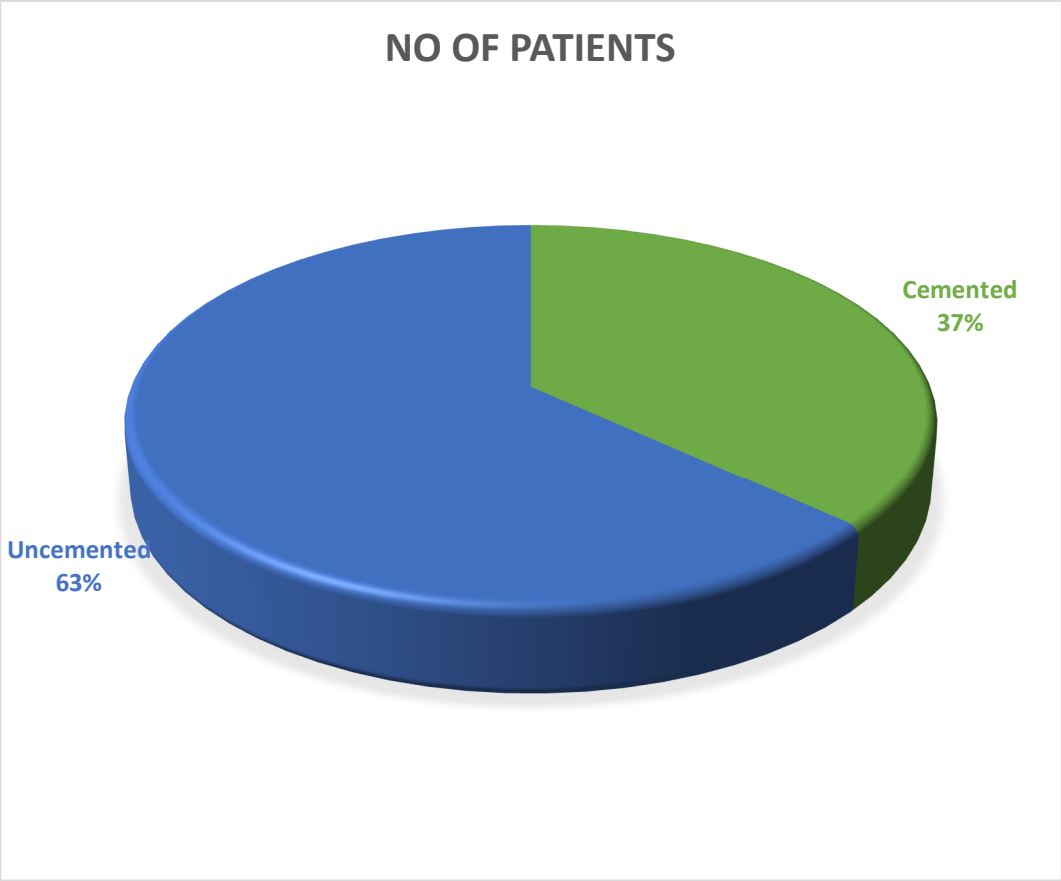
There was no noticeable difference in the blood levels of serum titanium levels with respect to gender. The sex distribution is represented in a graphical chart below:



## TYPE OF THR

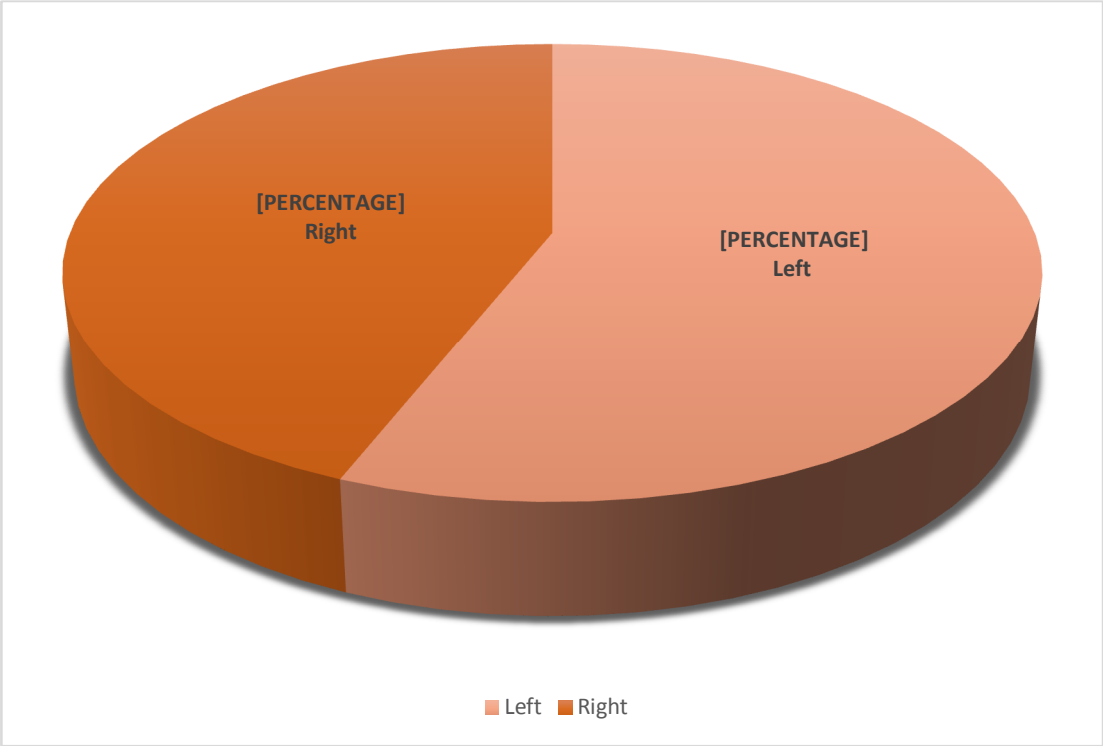
| Type of THR | No of patients |
|---|---|
| Cemented | 7 |
| Uncemented | 12 |

No difference in the serum level of titanium noted in patients of cemented or uncemented hemiarthroplasty.



## SIDE OF THE IMPLANT

| SIDE | No of patients |
|---|---|
| Left | 14 |
| Right | 11 |




**Side of implant did not have any effect on serum level titanium.**

Among the patients who were treated with the titanium implants

- 1 patient with bilateral total hip replacement who is a known case of systemic lupus erythematosis continued to have skin lesions, has increased levels of titanium compared to other patients but it was within the normal limit.
- 4 patients out of which 3 females and 1 male patient continued to have pain in the operated hip for which they were taking medications.
- All patients were ambulatory except 2 who had become bed ridden due to other comorbid medical conditions.
- 4 patients developed serum creatinine levels of above 1.6 mg/dl out of which 3 were hypertensive and 1 was diabetic.
- Serum alkaline phosphatase of 1 patient was mildly elevated which was not significant.
- 3 patients that is 2 male and 1 female patient had developed decreased vision due to cataract.
- 1 patient had loosening of dentures and artificial dentures was used which was accounted to age related degeneration.

- 2 paediatric patients who had titanium elastic nails developed mild itching over the operative site which was later subsided with medication.

- 1 patient had pus discharge through a sinus tract and was given a thorough wound wash with appropriate antibiotic which was subsided later.

- No significant age or sex related changes in serum levels of metal ions seen.

- No other specific toxicity signs were noted.

# DISCUSSION

J.Jacob et al[6] in his study of 42 patients in Chicago has also got a mean serum level of titanium within the normal limit. This study was performed in the year 1991 and the instrument used for the analysis was atomic absorption spectrometry. Two samples were used to analysis that is serum and urine. And the mean duration of estimation was thirty to forty months from the date of surgery. Other metals which were analysed in the study are vanadium and aluminium. In our study we have used inductively coupled plasma mass spectrometry as an instrument for the analysis of the samples. It has a detection level upto 0.002 microgram/Litre. And estimation was done by using only serum.

The use of titanium orthopaedic implants irrespective of unilateral or bilateral total hip replacement did not cross the normal serum levels in our study and this inference was similar to that obtained by Patrick Boyer et al [17](2009) who in his study of 134 patients of total hip replacement, mean value of serum titanium level was 0.72 microgram/Litre. The study contained both cemented and uncemented total hip replacement patients. The average follow up period was around 9 years with the maximum upto 12 years. Fifty three female and fifty six males were included in his study. The prosthesis used was made up of titanium alloy TiAl6V4 and it also contained titanium dioxide as a coating. All prosthesis were from the

Zimmer company. After the sample processing it was analysed under the inductively coupled optical emission spectrometry. The detection limit for the instrument was 30nmol/Litre. Other metal elements detected in their study was cobalt and chromium. In comparison to our study the prosthesis was made of Ti6Al4V ISO 5832-3 polarstem (femoral component) and the acetabular component reflection 3/no hole with Co-Cr. And all the prosthesis used were of Smith and nephew company. The average duration of sampling was six months.

Sean McGarry et al [18] in his study of 32 patients in Colorado in patients who have undergone intramedullary interlocking femur nailing by using titanium implant found a mean serum titanium level of 49.38 microgram/Litre. The study had 10 women and 22 men with a follow up period of 12 months. The titanium alloy used here was Ti6Al7Nb. The instrument used for the analysis of samples were inductively coupled plasma mass spectrometry. Even if fretting and corrosions had occurred in many cases of the femur nail patients it did not cause major elevation of the blood levels of the metal. And one of the reason attributable to it was the absence of synovial fluid in case of femur nail as in hip arthroplasty where in joint fluid may cause for the corrosion. And the serum level of metal did not cause any toxic signs or symptoms during follow up period. The study which we did where in the instrument used

was similar to the above study with high sensitive levels for detection revealed that the levels of titanium were within the normal limits.

Albercht Hartmann et al [19] in his study of various epidemiological studies has revealed that the patients undergoing metal on metal total hip arthroplasties are at an increased risk for developing higher metal ion levels in the blood. One of the finding was stemmed large head metal on metal prosthesis had an increased level than others. In the above study they have mentioned that besides local biological tissue reactions it is important to know about the teratogenicity, toxicity and carcinogenicity of the wear and tear materials released from the implants and their long term biological effect on various systems. They have also mentioned that until now the epidemiological studies have not revealed clinically relevant damage to cardiac, renal or nervous system after metal on metal total hip replacement. In our study too it was similar to Albertch Hartmann et al study in not having any toxicity attributable to the increase in the serum titanium levels.

# CONCLUSION

Mean serum titanium levels of all the patients was within the normal range and did not show any toxic signs or symptoms which could be directly attributed to rise in serum level.

Among the patients who had total hip replacement bilateral hip replaced patient showed an elevated serum level compared to unilateral patients.

Age, sex and side of the patient did not show any changes in the final outcome of serum levels of the titanium.

Both cemented and uncemented total hip replacement patients had nearly equal amount of serum titanium levels at the time of measurement.

In our study inductively coupled plasma mass spectrometry was used for the analysis which has increased sensitivity so comparison with similar technique may help for better correlation of results.

A large multicentric study would help in a better correlation of serum titanium levels and their toxicity upon various organs and systems over variety of region and race in different parts of the world.

## LIMITATIONS

Serial follow up level of the serum titanium was not measured. Size of the sample is smaller. Neurological and higher mental function tests were not performed in our study.

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# ANNEXURE - I

## ABBREVIATIONS

| | | |
|---|---|---|
| APC | : | Antigen presenting cell |
| Co | : | Cobalt |
| Cr | : | Chromium |
| GM-CSF | : | Granulocyte monocyte colony stimulating factor |
| IFN | : | Interferon |
| IL | : | Interleukin |
| MCP | : | Monocyte chemoattractant protein |
| MHC | : | Major histo compatibility |
| MMP | : | Matrix metallo proteinase |
| Ni | : | Nickel |
| NK | : | Natural killer cell |
| TCR | : | T cell receptor |
| TGF | : | Transforming growth factor |
| Ti | : | Titanium |
| TNF | : | Tumour necrosis factor |
| TRAP | : | tartarate resistant acid phosphatase |
| V | : | Vanadium |

## ANNEXURE – II

## THESIS PROFORMA

**SERUM TITANIUM ESTIMATION IN POST OPERATIVE INDIVIDUALS WITH TITANIUM IMPLANT USING INDUCTIVELY COUPLED MASS SPECTROMETRY AND ITS CLINICAL CORRELATION**

| | | |
|---|---|---|
| **Patient Name :**<br>**Age :** | **Sex : M/ F / TG** | |
| **Occupation :** | | **IP NO :** |
| **Address :** | **Contact no :** | |
| **Unit :** | **Professor :** | |
| **DOA :** | **DOS :** | **DOD :** |
| **Diagnosis :**<br>**Procedure :** | | |

**Implant Used :**

**Background Data :**

Smoking :

Alcohol :

Others :

| Follow up Date | SERUM TITANIUM LEVELS | Remarks |
|---|---|---|
| Post op | | |

**Clinical condition** :

Skin :

Allergic reactions :

Other symptoms :

**Signature of Professor**

# ANNEXURE – III

ஒப்புதல் படிவம்

பெயர் :

பாலினம் :

வயது :

முகவரி :

அரசு கோவை மருத்துவக் கல்லூரியில் எலும்பு முறிவு மருத்துவ துறையில் பட்ட பயிலும் மாணவன் அவர்கள் மேற்கொள்ளும் **"SERUM TITANIUM ESTIMATION IN POSTOPERATIVE INDIVIDUALS WITH TITANIUM IMPLANT USING INDUCTIVELY COUPLED PLASMA MASS SPECTROMETRY AND ITS CLINICAL CORRELATION"** குறித்த ஆய்வில் செய்முறை மற்றும் அனைத்து விவரங்களையும் கேட்டுக் கொண்டு எனது சந்தேகங்களை தெளிவுப்படுத்திக் கொண்டேன் என்பதை தெரிவித்துக் கொள்கிறேன்.

நான் இந்த ஆய்வில் முழு சம்மதத்துடன், சுய சிந்தனையுடனும் கலந்து கொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வில் என்னுடைய அனைத்து விபரங்கள் பாதுகாக்கப்படுவதுடன் இதன் முடிவுகள் ஆய்விதழில் வெளியிடப்படுவதில் ஆட்சேபனை இல்லை என்பதை தெரிவித்துக் கொள்கிறேன். எந்த நேரத்திலும் இந்த ஆய்விலிருந்து நான் விலகிக் கொள்ள எனக்கு உரிமை உண்டு என்பதையும் அறிவேன்.

## ANNEXURE – IV

## MASTER CHART

| SI.NO | NAME | AGE/SEX | IP.NO | DIAGNOSIS | PROCEDURE | DATE OF SURGERY | DATE OF SAMPLE COLLECTION | COMORBIDITIES | CLINICAL SYMPTOMS | SERUM Ti LEVEL (microgram/L) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. | CHITRA | 23/F | 34707 | B/L AVN OF HIP WITH SLE | B/L CEMENTED TOTAL HIP REPLACEMENT | 25/7/16 | 20/6/17 | SLE | SKIN HYPOPIGMENTATION FINGERTIPS,TOES,FACE | 1 |
| 2. | RENUGADEVI | 55/F | 36819 | # NECK OF FEMUR LEFT | TOTAL HIP REPLACEMENT LEFT | 18/6/16 | 25/12/16 | NIL | NIL | 1.02 |
| 3. | AMMASAIKUTTY | 65/F | 44388 | # NECK OF FEMUR RIGHT | TOTAL HIP REPLACEMENT RIGHT | 9/7/16 | 2/3/17 | DIABETIC | CATARACT, PAIN OVER OPERATIVE SITE | 0.16 |
| 4. | ANANDARAJ | 52/M | 46218 | # NECK OF FEMUR LEFT | CEMENTED TOTAL HIP REPLACEMENT LEFT | 21/3/17 | 5/10/17 | NIL | ITCHING OVER SCAR | 0.89 |
| 5. | NAGAMANI | 66/M | 33751 | # NECK OF FEMUR RIGHT | CEMENTED TOTAL HIP REPLACEMENT RIGHT | 29/5/16 | 12/12/16 | NIL | PUS DISCHARGE | 0.4 |
| 6. | MARAGATHAM | 56/F | 37059 | # NECK OF FEMUR LEFT | TOTAL HIP REPLACEMENT LEFT | 21/7/16 | 6/3/17 | HYPERTENSIVE | PAIN IN OPERATED HIP | 0.3 |
| 7. | ALPHONSE K | 52/M | 69955 | # NECK OF FEMUR LEFT | TOTAL HIP REPLACEMENT LEFT | 3/1/17 | 6/6/17 | HYPERTENSIVE | SKIN DISCOLOURATION OVER OPERATIVE SITE | 0.27 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 8. | ARUMUGAM | 66/M | 5910 | AVASCULAR NECROSIS LEFT FEMUR HEAD | CEMENTED TOTAL HIP REPLACEMENT LEFT | 23/3/16 | 30/9/16 | NIL | PAIN IN OPERATED HIP | 0.2 |
| 9. | GANESAN | 39/M | 24607 | # NECK OF FEMUR LEFT | TOTAL HIP REPLACEMENT LEFT | 23/6/16 | 12/1/17 | NIL | PUS DISCHARGE FOR FEW 4 WEEKS | 0.11 |
| 10. | PALANI | 70/M | 34819 | # NECK OF FEMUR RIGHT | CEMENTED TOTAL HIP REPLACEMENT RIGHT | 11/6/16 | 9/1/17 | HYPERTENSIVE | CATARACT | 0.29 |
| 11. | MARIMUTHU | 53/M | 30783 | # NECK OF FEMUR RIGHT | TOTAL HIP REPLACEMENT RIGHT | 22/5/16 | 14/12/16 | NIL | SKIN RASHES OVER OPERATIVE SITE | 0.13 |
| 12. | SATYANARAYANAN | 43/M | 16865 | # NECK OF FEMUR LEFT | TOTAL HIP REPLACEMENT LEFT | 2/4/16 | 16/11/16 | HYPERTENSIVE | NIL | 0.42 |
| 13. | SURESH | 50/M | 52927 | # NECK OF FEMUR RIGHT | TOTAL HIP REPLACEMENT RIGHT | 30/9/16 | 2/5/17 | SMOKER,COPD | NIL | 0.14 |
| 14. | SELVARAJ | 80/M | 51782 | # NECK OF FEMUR RIGHT | CEMENTED TOTAL HIP REPLACEMENT RIGHT | 13/9/16 | 21/4/17 | ASTHMA, HYPERTENSIVE | DECREASED HEARING | 0.17 |
| 15. | SHANTHAMANI | 50/F | 36410 | # NONUNION NECK OF FEMUR RIGHT | TOTAL HIP REPLACEMENT RIGHT | 7/7/16 | 23/2/17 | DIABETIC | CATARACT | 0.08 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 16. | MURUGESAN | 45/M | 13871 | # NECK OF FEMUR LEFT | TOTAL HIP REPLACEMENT LEFT | 3/6/16 | 6/1/17 | NIL | NIL | 0.12 |
| 17. | DHANALAKSHMI | 63/F | 23926 | # NECK OF FEMUR LEFT | CEMENTED TOTAL HIP REPLACEMENT LEFT | 20/6/16 | 13/1/17 | HYPERTENSIVE | DENTURE LOOSENING | 0.08 |
| 18. | MOHAN | 50/M | 35498 | #NONUNION NECK OF FEMUR RIGHT | TOTAL HIP REPLACEMENT RIGHT | 12/10/16 | 3/5/17 | NIL | NIL | 0.07 |
| 19. | VAIDEESHWARAN | 9/M | 36152 | #SHAFT OF FEMUR LEFT | TENS NAILING | 3/3/17 | 12/9/17 | NIL | ITCHING OVER MEDIAL SIDE | 0.07 |
| 20. | ASHWIN | 6/M | 82370 | #SHAFT OF FEMUR LEFT | TENS NAILING | 9/8/17 | 4/5/18 | NIL | NIL | 0.12 |
| 21. | NIVEDHA | 11/F | 13098 | #SHAFT OF FEMUR RIGHT | TENS NAILING | 4/1/18 | 1/5/18 | NIL | NIL | 0.12 |
| 22. | KOWSIKA | 7/F | 63979 | #SHAFT OF FEMUR LEFT | TENS NAILING | 14/10/16 | 12/5/17 | NIL | DISCHARGE AT ENTRY SITE | 0.09 |
| 23. | BRINDA | 8/F | 75305 | #SHAFT OF FEMUR LEFT | TENS NAILING | 30/11/16 | 6/6/17 | NIL | NIL | 0.09 |
| 24. | KAVYA | 8/F | 65382 | #SHAFT OF FEMUR RIGHT | TENS NAILING | 13/1/18 | 21/5/18 | NIL | SKIN DISCOLOURATION AT ENTRY SITE | 0.13 |
| 25. | RESHMA | 9/F | 51694 | #SHAFT OF FEMUR RIGHT | TENS NAILING | 19/8/16 | 18/3/17 | NIL | ITCHING OVER OPERATIVE SITE | 0.09 |